STUDIES ON THE SYNTHESIS AND TRANSFORMATIONS OF A FEW 2(3H)- AND 3(2H)-FURANONES

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IN THE FACULTY OF SCIENCE

BY

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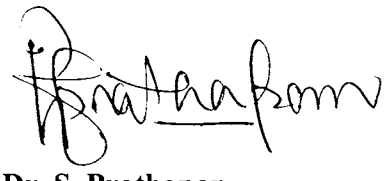
CERTIFICATE

This is to certify that the thesis herewith is an authentic record of research work carried out by the author under my supervision, in partial fulfilment of the requirements for the degree of Doctor of Philosophy of Cochin University of Science and Technology, and further that no part thereof has been presented before for any other degree.



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LIST OF SPECTRA

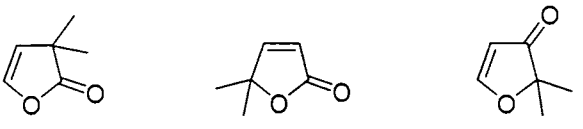
ABSTRACT

The thesis entitled **'Studies on the synthesis and transformations of a few 2(3H)- and 3(2H)-furanones'** is divided into 9 chapters.

In **Chapter 1**, a review on the synthesis and transformations of various 2(3H)-, 2(5H)- and 3(2H)-furanones is presented. **Chapter 2** deals with our endeavors on the synthesis of 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones. **Chapter 3** discusses our attempts to synthesis 5-aryl-3,3-dipyridin-2-yl-3H-furan-2-ones. **Chapter 4** presents synthesis of 2-acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones. **Chapter 5** deals with our experiments to synthesis 2-aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones. **Chapter 6** mainly deals with the synthesis of 2- aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones. **Chapter 7** describes the photochemical transformations of 3,3-bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones. **Chapter 8** describes the thermal and photochemical transformations of 3(2H)-furanones. **Chapter 9** deals with the biological studies on a few 3(2H)-furanones.

Chapter 1: Synthesis and Transformations of Various 2(3H)-, 2(5H)- and 3(2H)-Furanones - A Historical Appraisal

Furanones represent an interesting class of heterocyclic compounds, which constitute the central ring system of many natural products. They are derivatives of furan and, depending on structure, are divided into three main types: 2(3H)-furanones (**I**), 2(5H)-furanones (**II**), and 3(2H)-furanones (**III**). The IUPAC-approved names for these heterocycles are 2,3-dihydrofuran-2-ones, 2,5-dihydrofuran-2-ones and 3,2-dihydrofuran-3-ones respectively (Figure.1).



2(3H)-furanone **I** 2(5)-furanone **II** 3(2H)-furanone **III**

Figure 1

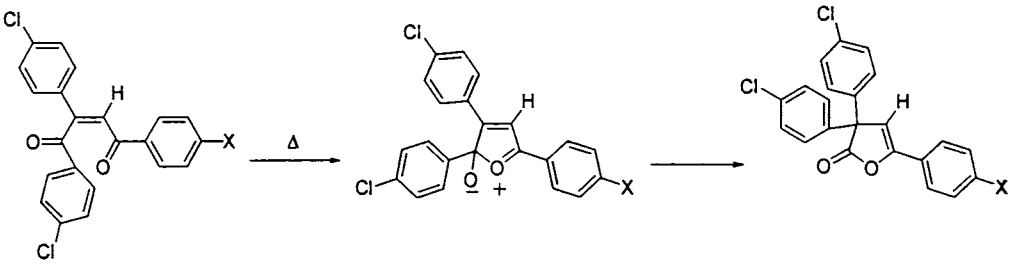
Systems **I** and **II** are unsaturated γ-lactones known as 'butenolides'. Compounds of this type are also known as 'crotonolactones' based on the parent crotonic acid.

The compounds originate in several ways: they are produced by living things directly, they arise as a result of the processing of biological materials, or they form in the environment from organic matter under certain circumstances.

In light of enormous interest in the versatile utility of these classes of heterocyclic compounds, numerous synthetic efforts have been directed towards these substances. A brief survey of the major synthetic routes and various transformations of these furanones are provided in this chapter.

Chapter 2: Synthesis of 5-Aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones

In order to explore the effect of the nature of aryl groups present at the 3-position in controlling reactivity of 2(3H)-furanones, we proposed to synthesise various 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones. The method we adopted involved the base catalysed condensation of 4,4'-dichlorobenzil with suitably substituted acetophenones to give diaroylstyrenes which upon thermolysis yield the corresponding 2(3H)-furanones. In this chapter, we describe our endeavours on the synthesis and characterisation of several 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones (Scheme A 1).



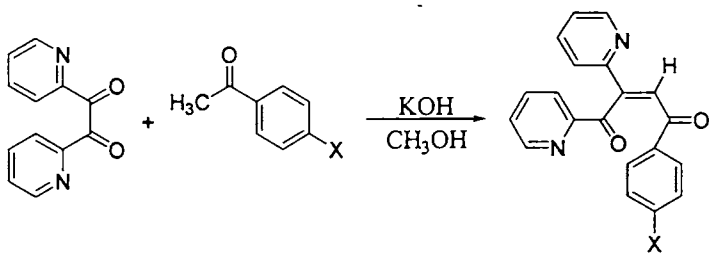
5a-d **6a-d** **7a-d**

a) X = H c) X = CH_3
b) X = Cl d) X = OCH_3

Scheme A 1

Chapter 3: Attempted Synthesis of a Few 5-Aryl-3,3-dipyridin-2-yl-3H-furan-2-ones

In continuation with our studies on 2(3H)-furanones and in order to examine the influence of heteroaromatic substituents on the photochemical pathways followed by 2(3H)-furanones, we proposed to synthesise a few 3,3.5-triaryl-2(3H)-furanones having heteroaromatic substituents. Based on the previous reports on the thermal transformations of dibenzoylstyrenes, we identified 4-phenyl-1,2-dipyridin-2-yl-but-2-ene-1,4-dione **3** as a potential precursor to the required furanone derivative. In this chapter, we describe the synthesis of several 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-dione precursors by the base-catalysed reaction between 2,2'-pyridil and suitably substituted acetophenones (Scheme A 2). These novel dibenzoylalkenes-type systems containing heteroartomatic rings underwent extensive decomposition under the influence of heat.



1 **2 a-h** **3 a-h**

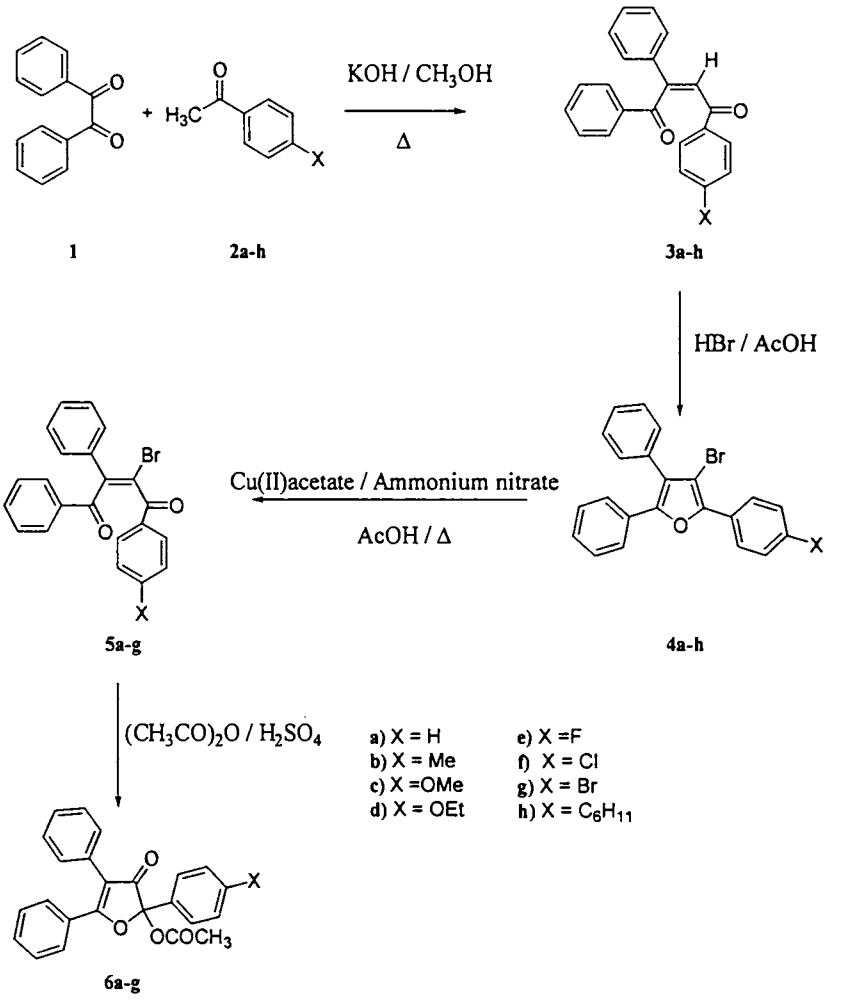
a) X = H
b) X = CH_3
c) X = OCH_3
d) X = OEt
e) X = F
f) X = Cl
g) X = Br
h) X = C_6H_{11}

Scheme A 2

Chapter 4: Synthesis of 2-Acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones

While most of the investigations on 2(3H)- and 2(5H)-furanones were directed at unraveling the mechanistic underpinnings of their remarkable photochemistry, 3(2H)-furanones were investigated for their potential antitumor activity. As a logical extension of our continued interest in the synthesis and chemistry of dibenzoylalkenes and dibenzoylalkene-type systems, we targeted the synthesis of 3(2H)-furanones from dibenzoylalkene precursors. The protocol

developed by us employed readily available dibenzoylalkenes as starting materials and provided easy access to differently functionalised 3(2H)-furanones in four steps (Scheme A 3). The structure of these acetoxyfuranones was established on the basis of X-ray diffraction studies. The synthesis of a few 2-acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones is discussed in this chapter.

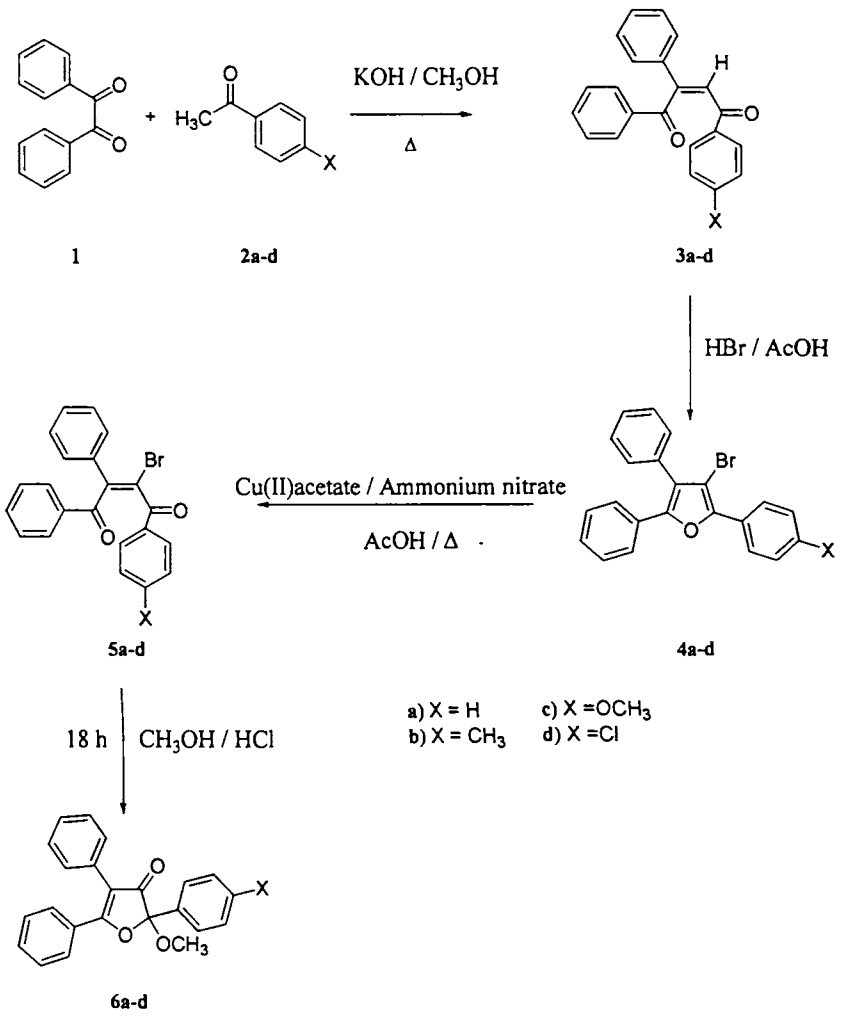


Scheme A 3

Chapter 5: Synthesis of 2-Aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones

In the previous chapter we have described the simple and facile route for the synthesis of 3(2H)-furanones from dibenzoylalkene precursors. After the successful synthesis and establishment of the structure of 2-acetoxy 3(2H)-furanones, there has been a continued interest in the synthesis of another series of 3(2H)-furanone by introducing a methoxy substituent at 2- position of the furanone

ring. 2-Methoxy-3(2H)-furanones can be conveniently prepared by treating *(E)*-1-Aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-diones with methanol saturated with hydrogen chloride gas. Our endeavors on the synthesis 2-aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones from the corresponding *(E)*-bromodibenzoylalkenes is discussed in this chapter (Scheme A 4).

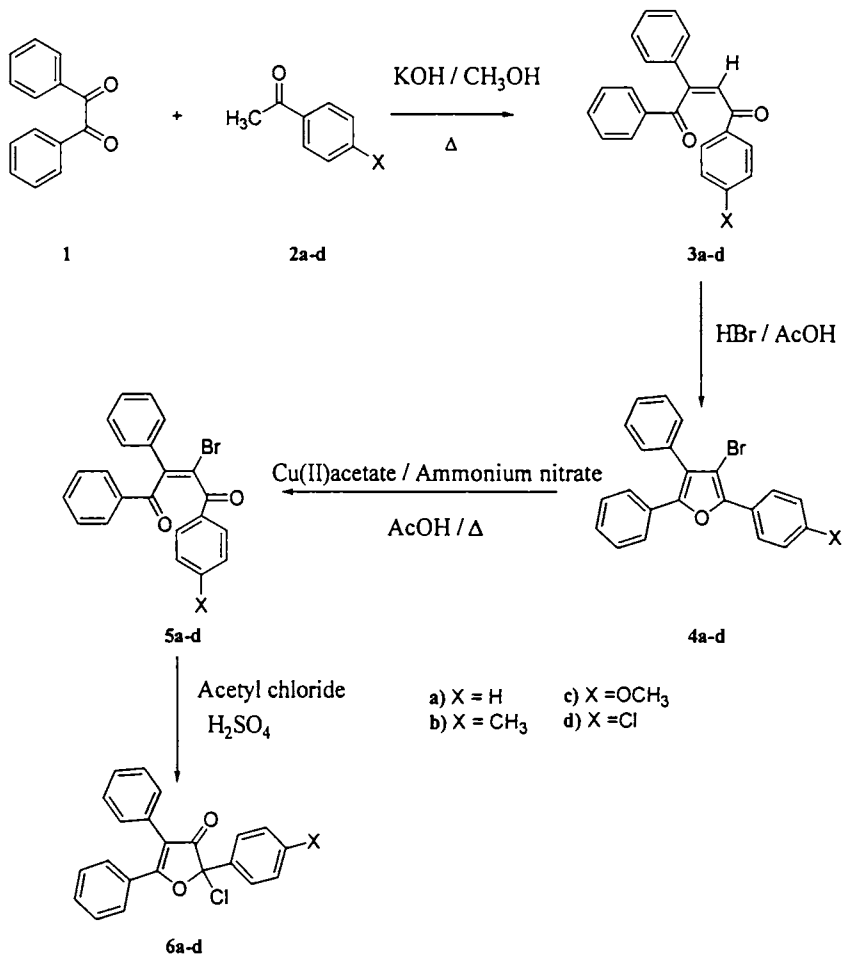


Scheme A 4

Chapter 6: Synthesis of 2-Aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones

Our persisting interest in the chemistry of 3(2H)-furanones encouraged us to synthesis yet another class of 3(2H)-furanones by varying the substituent at the 2-position of the furanone ring. Thus in conjunction with our studies on furanones, we synthesised 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones from dibenzoylalkene precursors. *(E)*-Bromodibenzoylalkenes on reaction with acetyl

chloride in presence of catalytic amount of concentrated sulphuric acid yield 2-chloro-3(2H)-furanones (Scheme A 5). This chapter presents the syntheses of several 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones from the corresponding bromodibenzoylalkene precursors.

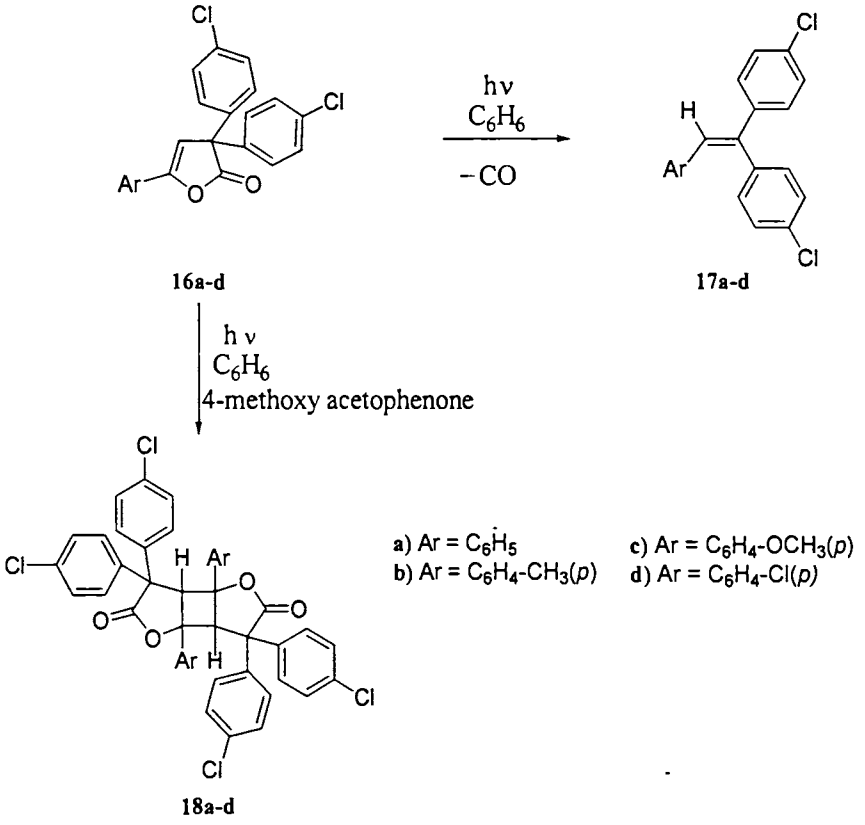


Scheme A 5

Chapter 7: Photochemical Transformations of 3,3-Bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones

Photochemical transformations of several 2(3H)-furanones have been investigated in detail. It has been reported that unsaturated lactones undergo a variety of phototransformations such as decarbonylation, decarboxylation, solvent addition to double bonds, migration of aryl substituents and dimerisation. In the present study we have examined the singlet and triplet mediated photochemical transformations of 5-aryl-3,3-bis(4-chlorophenyl)-2(3H)-furanones with a view to

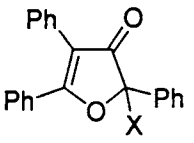
understand the effect of substituents at the 3 and 5 positions of furanones on their phototransformations. On direct irradiation these aryl substituted 2(3H)-furanones underwent decarbonylation to yield corresponding α,β-unsaturated carbonyl compounds and upon sensitised irradiation they underwent dimersation arising through a 2+2 cycloaddition reaction (Scheme A 6).



Scheme A 6

Chapter 8: Thermal and Photochemical Transformations of 3(2H)-Furanones

As a part of our ongoing interest in the synthesis and transformations of triarylfuranones, and on the basis of the information generated on the photochemical transformations of a few 2(3H)-furanones, we decided to investigate the thermal and photochemical transformations of triaryl-3(2H)-furanones **1a-c** synthesised by us (Figure 2). While these compounds exhibited thermal stability, they underwent extensive decomposition to intractable mixtures under the influence of light.



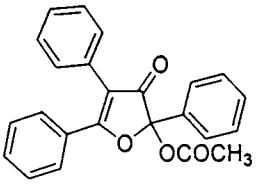
a) X = $OCOCH_3$
b) X = OCH_3
c) X = Cl

1

Figure 2

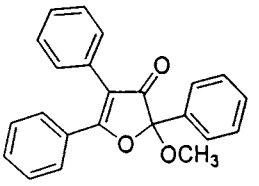
Chapter 9: Biological Studies of a few 3(2H)-Furanones

The anti-proliferative effect of the newly synthesised 3(2H)-furanones (Figure 3) was studied by examining their action on tumor cells. Both *in vitro* and *in vivo* experiments were done for the assessment of anti-proliferative effect. The *in vitro* experiments indicated that compounds **1** and **2** significantly inhibit the proliferation of Daltons Lymphoma Ascites (DLA) cell line (Table 1). The effect of these compounds on tumor-bearing mice was also studied and the result showed that the administration of **1**, **2** and **3** synthesised by us could significantly prevent the growth of tumor compared to the control animals, which did not receive these compounds (Figure 4). This chapter deals with the *in vitro* and *in vivo* antumor studies on a few 3(2H)-furanones synthesized by us. *In vivo* and *in vitro* studies of these 3(2H)-furnaones showed significiant inhibition of tumor cell proliferation.



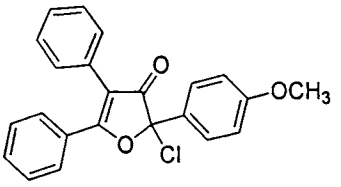
2-Acetoxy-2,4,5-triphenyl-2-H-furan-3-one

1



2-Methoxy-2,4,5-triphenyl-2-H-furan-3-one

2



2-Chloro-2-(4-methoxyphenyl)-4,5-diphenyl-2H-furan-3-one

3

Figure 3

Effect of various concentrations of compound 1 and 2 on Thymidine incorporation to DNA (DPM/mg protein) of DLA cell line *in vitro*

Compound	Control	10 µg	20 µg	50 µg	100 µg	200 µg
1	34329 ± 116	23350 ± 201***	22086 ± 463***	20186 ± 267***	19539 ± 212***	17737 ± 252***
2	34329 ± 116	22924 ± 304***	23824 ± 163***	22349 ± 377***	17485 ± 252***	17478 ± 522***

Values are mean ± S.E.M. of 4-6 separate experiments

***$p<0.001$ when compared to control

Table 1

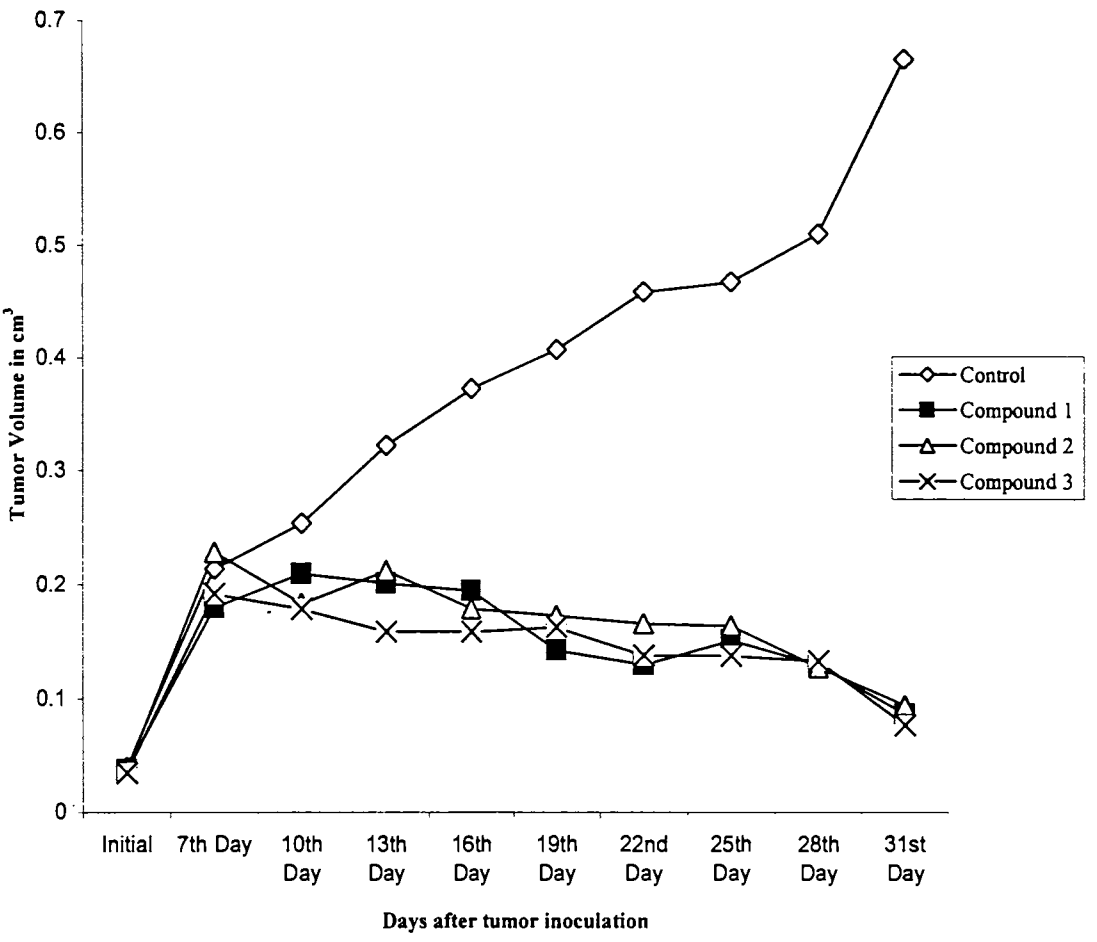


Figure 4

In conclusion a number of 2(3H)- and 3(2H)-furanones were synthesised from dibenzoylalkene precursors and were charecterised on the basis of spectral, analytical and X-ray data. On direct irradiation 3,3-bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones underwent decarbonylation to yield the corresponding α,β-unsaturated carbonyl compounds and upon sensitised irradiation they underwent dimersation arising through a 2+2 cycloaddition reaction. Our studies on 3(2H)-furanones revealed that these compounds are thermally stable, while they undergo extensive decomposition to intractable mixtures under the influence of light. Similarly, the novel dibenzoylalkenes-type systems containing heteroatomatic rings synthesised by us also underwent extensive decomposition under the

influence of heat. Some of the 3(2H)-furanones synthesised by us exhibit remarkable anti-proliferative activity.

Note: The numbers given to various compounds herein correspond to those given in respective chapters. We have reported only the relevant data for the characterisation of novel compounds synthesised by us.

Chapter 1

SYNTHESIS AND TRANSFORMATIONS OF VARIOUS 2(3H)-, 2(5H)- AND 3(2H)-FURANONES - A HISTORICAL APPRAISAL

In this chapter, a concise review on the synthesis and transformations of 2(3H)-, 2(5H)- and 3(2H)-furanones is presented.

1.1. Introduction

As a science in its own right, organic synthesis emerged at the beginning of the last century, when chemists started to master the skills of manipulating compounds in a controlled and predictable fashion, which eventually elaborate as arsenal of tools required for the preparation of various target products from simple starting materials. The spectacular progress achieved from this complemented by the discovery of new approaches to the analysis of synthetic problems, changed the very image of organic synthesis dramatically. Modern organic synthesis, with its spirit of most daring endeavor, coupled with the craftsmanship of the design and assemblage of diverse molecular structures of formidable complexity, may serve as a convincing illustration to the prophetic claims of M. Berthelot (1860) about the intrinsic capacity for creation as a distinctive feature of science of chemistry.

The known organic compounds have an enormous diversity of structure. Many of these structures contain ring systems. If the ring system is made up of atoms of carbon and atleast one other element, the compound is classed as *heterocyclic.* The elements that occur most commonly, together with carbon, in ring systems are nitrogen, oxygen and sulphur. About the half of known organic compounds have structures that incorporate atleast one heterocyclic component.[1]

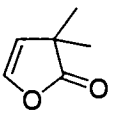
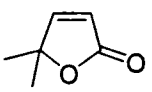
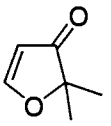
Heterocyclic compounds have a wide range of applications: they are predominant among the types of compounds used as pharmaceuticals, agrochemicals and veterinary products.[2] Heterocyclics are used as optical

brightening agents, antioxidants, corrosion inhibitors and additives with a variety of other functions. Many dyes and pigments have heterocyclic ring components.

One of the reasons for the widespread use of heterocyclic compounds is that their structures can be subtly manipulated to achieve a required modification in function. An important feature of the structure of many heterocyclic compounds is that it is possible to incorporate functional groups either as substituent or as a part of the ring system itself. These compounds are also finding an increasing use as intermediates in organic synthesis. [3-5] Very often this is because a relatively stable ring system can be carried through a number of synthetic steps and then cleaved at the required stage in a synthesis to reveal other functional groups.

Heterocyclic compounds are widely distributed in nature, and are of fundamental importance to living systems. Chlorophyll and heme are two of the most celebrated examples of biologically active compounds possessing complex heterocyclic ring components. Many of the pharmaceuticals and most of the other heterocyclic compounds with practical applications are not extracted from natural sources but are manufactured. It is not surprising, therefore, that a great deal of current research work is concerned with methods of synthesis and examining the properties of heterocyclic compounds. A detailed discussion of the chemistry of heterocyclic compounds is beyond the scope of this thesis. In this chapter, the discussion is limited to one important class of heterocycles: the furanones.

Furanones represent an interesting class of heterocyclic compounds, which constitute the central ring system of many of the natural products and may be reg. They are derivatives of furan and, depending on structure, are divided into three main types: 2(3H)-furanones (**I**), 2(5H)-furanones (**II**), and 3(2H)-furanones (**III**).[4] The IUPAC-approved names for these heterocycles are 2,3-dihydrofuran-2-ones, 2,5-dihydrofuran-2-ones [6]and 3,2-dihydrofuran-3-ones respectively (Figure.1). Both these nomenclatures are used interchangeably in this chapter and throughout the thesis.

2(3H)-furanone 2(5)-furanone 3(2H)-furanone

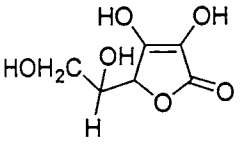
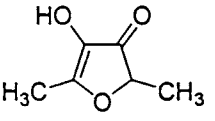
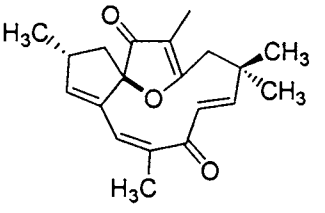
I **II** **III**

Figure 1

Systems **I** and **II** are unsaturated γ-lactones known as 'butenolides'. Compounds of this type are also known as 'crotonolactones' based on the parent crotonic acid. On the other hand, **III** is a cyclic α,β-unsaturated ketone.

The best known and most widely studied of naturally occurring furanones is ascorbic acid (vitamin C). This compound has been the subject of research for well over 100 years now and its involvement in many redox reactions in a range of organisms is well established.[6] A moderate number of furanones with a number of potent biological activities, in addition to ascorbic acid and related compounds have been found in animals,[7] plants,[8] microorganisms,[9] prepared foods [10]and water supplies.[11]

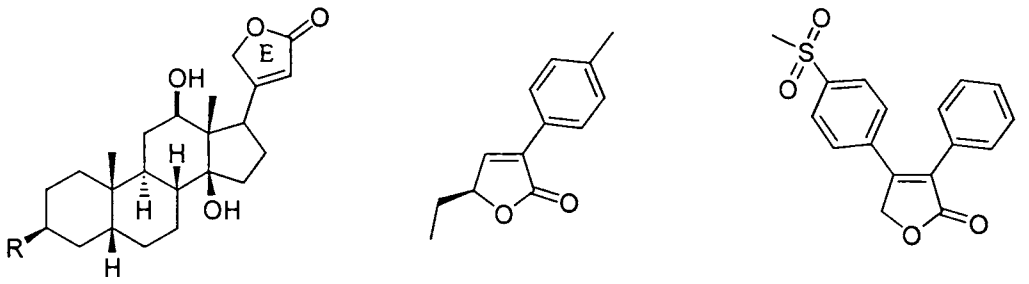
For human beings, furanones are important, as they are major attractive components of many food flavors such as strawberry,[12] pineapple,[13] roasted meat,[14] nuts, and soy sauce.[15] Some examples of naturally occurring as well as pharmaceutically relevant furanones are shown in figure 2 and 3.

L- Ascorbic acid 2,5-Dimethyl-4-hydroxy-3(2H)-furanone Jatrophone

Examples of naturally occuring furanones

Figure 2



Digitoxin Incrustoporine Rofecoxib

Examples of pharmaceutically relevant furanones

Figure 3

The compounds originate in several ways; they are produced by living things directly,[16] they arise as a result of the processing of biological materials, or they form spontaneously in the environment from organic matter under certain circumstances.[17]

In light of enormous interest in the versatile utility of these classes of heterocyclic compounds, numerous synthetic efforts have been directed towards these substances. A brief survey of the major synthetic routes to furanones is provided in the following section.

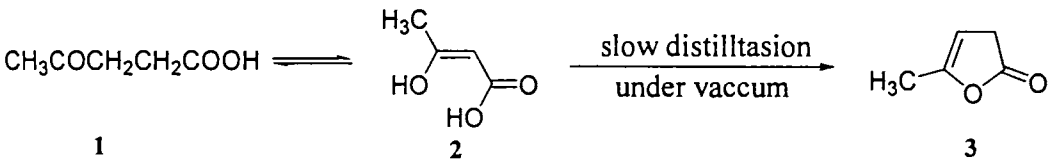
1.2. Methods of Preparation

1.2.1. Synthesis of 2(3H)-Furanones

Among butenolides, 2(3H)-furanones are most widely employed as useful synthetic units for C-C bond formation and introduction of functional groups. Various methods for the preparation of these lactones are well known.

1.2.1.1. From γ-Keto Acids. One of the common methods for the synthesis of 2(3H)-furanone involves the intramolecular dehydration of the corresponding γ-keto acids.[18-28]. Levulinic acid which can enolise readily, gives α-angelica lactone on slow distillation. The cyclisation can also be effected by

heating with acetic anhydride, acetyl chloride or a mixture of acetic anhydride and sulphuric acid (Scheme 1).

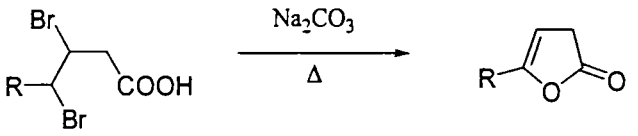


1 2 3

Scheme 1

However, reaction conditions employed in the above procedure; heating in acetic anhydride are sometimes too vigorous for other functional groups to survive and often bring about concomitant formation of isomeric 2(5H)-furanones.

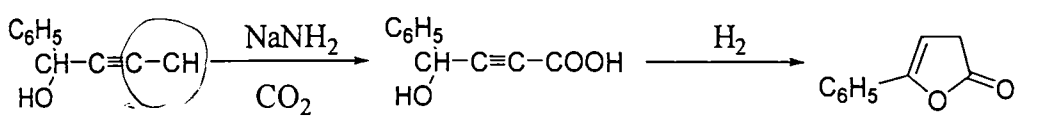
1.2.1.2. From β,γ-Dibromo Acids. 2(3H)-Furanones can be prepared from β,γ-dibromo acids **4** by treating with water or sodium carbonate solution.[29-31] The reaction proceeds through a hydrolysis - cyclisation - dehydrobromination sequence to give the furanone product. Thermal decomposition of **4** in presence of quinoline also led to the formation of these furanones (Scheme 2).



4 5

Scheme 2

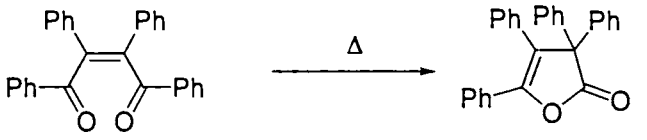
1.2.1.3. From Acetylenic Acids. Nineham *et al.* in 1949 have reported the synthesis of 2(3H)-furanones from acetylenic acids.[32] Carboxylation of phenylethynylcarbinol (**6**) in presence of sodamide gives 4-hydroxy-4-phenylbut-2-ynoic acid (**7**). Upon hydrogenation, **7** gives the corresponding 2(5H)-furanone, which isomerises to 5-phenyl-2(3H)-furanone (**8**). (Scheme 3).



6 7 8

Scheme 3

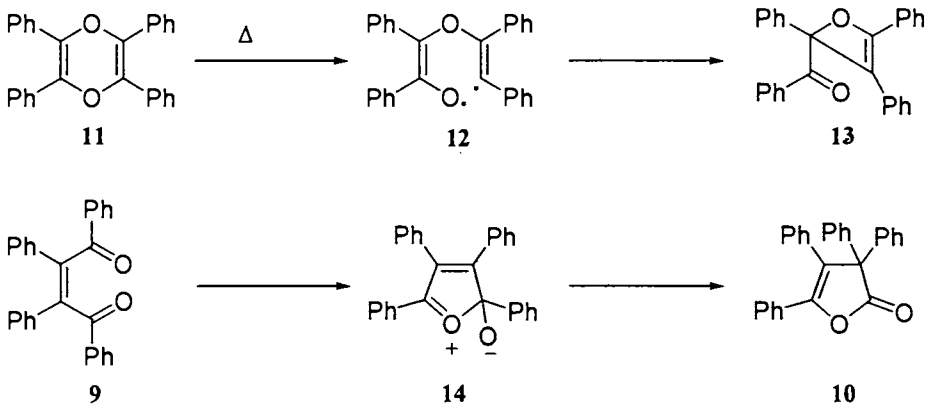
1.2.1.4. Thermal Rearrangement of Dibenzoylalkenes. Dibenzoylalkenes undergo bond reorganization process thermally to give corresponding 2(3H)-furanones.[33-36] This remarkable rearrangement was first observed by Zenin in 1872 when he established that pyrolysis of *cis*-dibenzoylstilbene **9**) led to the formation of tetraphenylcrotonolactone (**10**) (Scheme 4).



9 **10**

Scheme 4

Berger and Summerbell observed similar thermal rearrangements in the case of tetraphenyl-*p*-dioxadiene (**11**). Upon pyrolysis around 250 ^{0}C, **11** rearranges to tetraphenylcrotonolactone (**10**) through the intermediacy of dibenzoylstilbene (**9**) (Scheme 5).[37,38]

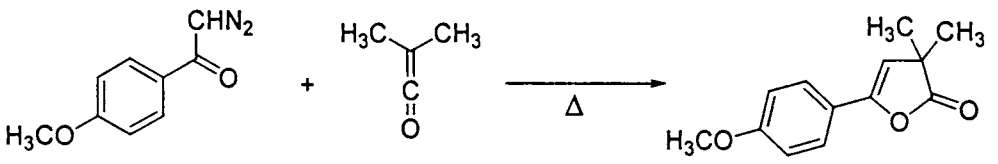


11 **12** **13**

9 **14** **10**

Scheme 5

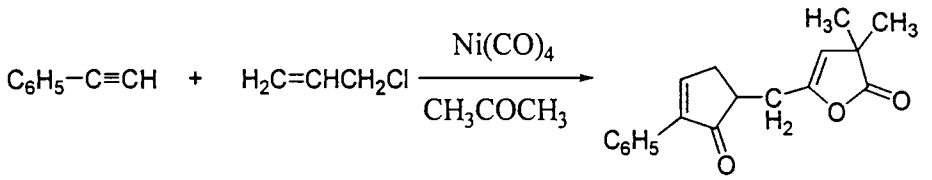
1.2.1.5. From Diazoketones and Ketene Derivatives. The reaction of diazoketones with ketenes in ether in N_2 atmosphere at room temperature has reported to give 2(3H)-furanones through 1,3-cycloaddition.[39-42] Dimethyl ketene on reaction with substituted diazoketones gives corresponding 2(3H)-furanone.[42] (Scheme 6).



15 16 17

Scheme 6

1.2.1.6. Metal Carbonyl Catalysed Reactions. Chiusoli and co-workers[43] reported the synthesis of 2(3H)-furanones from phenylacetylene and allyl halides in presence of nickel tetracarbonyl in acetone (Scheme 7).



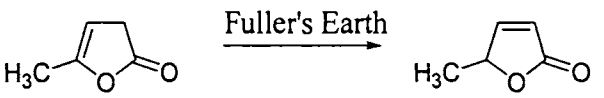
18 19 20

Scheme 7

Similar reactions were carried out with 1-hexyne and 1-octyne.[44]

1.2.2. Synthesis of 2(5H)-Furanones

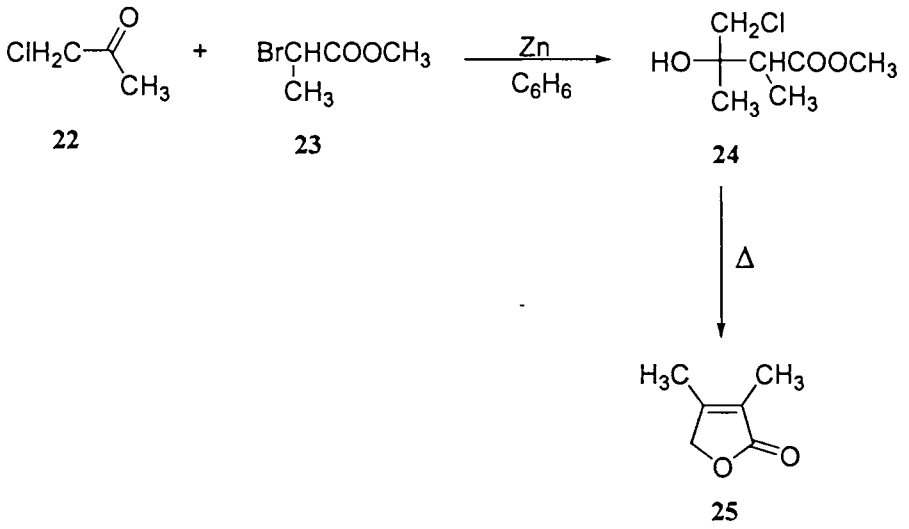
1.2.2.1. From 2(3H)-Furanones. By the action of bases such as triethylamine, piperidine, or even benzylamine, 2(3H)-furanones are converted to the corresponding 2(5H)-furanone through proton abstraction followed migration.[45-47] Acetic anhydride has also been employed to effect this isomerisation. On large scale, α-angelica lactone (**3**) is converted to β-angelica lactone (**21**) by passing its vapours over Fuller's earth.[48] (Scheme 8).



3 21

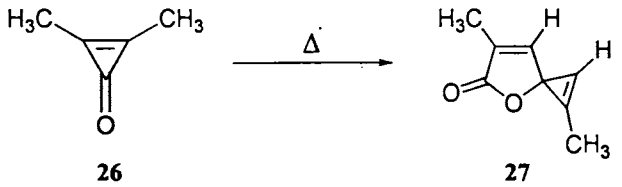
Scheme 8

1.2.2.2. By Reformatsky-Elderfield Reaction. The reaction of α-acetoxy ketones with bromoacetic esters under Reformatsky condition is one of the most common methods for the synthesis of 2(5H)-furanones and steroidal lactones.[49-70] A variation of the Reformatsky reaction has been employed by Epstein and Sonntag.[71,72] Instead of α-acetoxy ketones, α-halo ketones were reacted with bromoacetic ester in the presence of zinc to give unstable Reformatsky adducts which were converted to 2(5H)-furanones either by pyrolysis or by conversion to unsaturated hydroxymethyl esters and photolysis of the latter (Scheme 9).



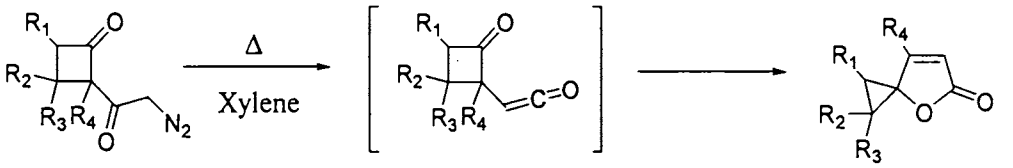
Scheme 9

1.2.2.3. Ring-Expansion Reactions. Strained ring compounds have recently attracted the interest of the synthetic organic chemist due to explosive development of the synthetic routes to highly functionalised starting materials. Substituted cyclopropenones on heating gives corresponding spirocyclopropyl-2(5H)-furanones.[73,74] (Scheme 10).



Scheme 10

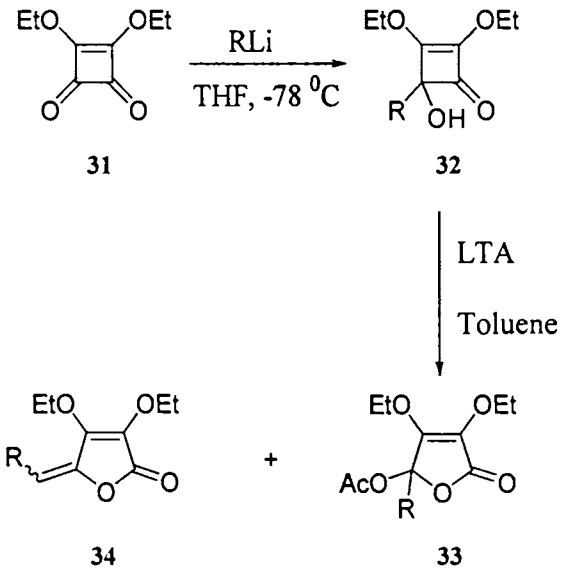
Squaric acid is a fascinating C_4-synthon. A wide variety of 3,4-disubstituted cyclobutenediones and 4-hydroxycyclobutenones are readily accessible from squaric acid, and further transformation of the modified cyclobutenones by thermolysis, photolysis, oxidative rearrangement and catalysis is aided by the relief of ring strain.[75-80.] Miller in 1991 reported the synthesis of 5-spirocyclopropyl-2(5H)-furanones **30** from 2-(diazoacetyl)cyclobutanones **28** via a facile stereospecific thermal rearrangement through α-ketenylcyclobutanone intermediate [76] (Scheme 11).



28 **29** **30**

Scheme 11

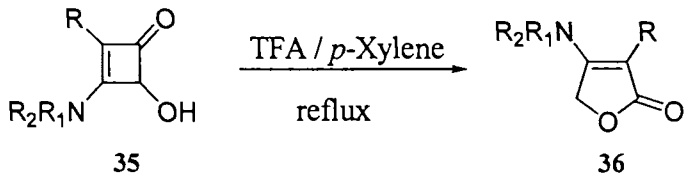
Yamomoto and co-workers [81] in 1995 selectively synthesized 2(5H)-furanone from 4-hydroxybutenediones by accomplishing ring opening by β-scission of radical generated at the position adjacent to the cyclobutene ring, and the subsequent 5-endo ring closure of the resulting acyl radical intermediate gave the desired product (Scheme 12).



31 **32** **34** **33**

Scheme 12

Wang et al in 2001 [82] reported a convenient sequence for the synthesis of 3-substituted 4-aminofuran-2(5H)-ones **36** from 4-hydroxycyclobutenone **35** and trifluoroacetic acid (Scheme 13).

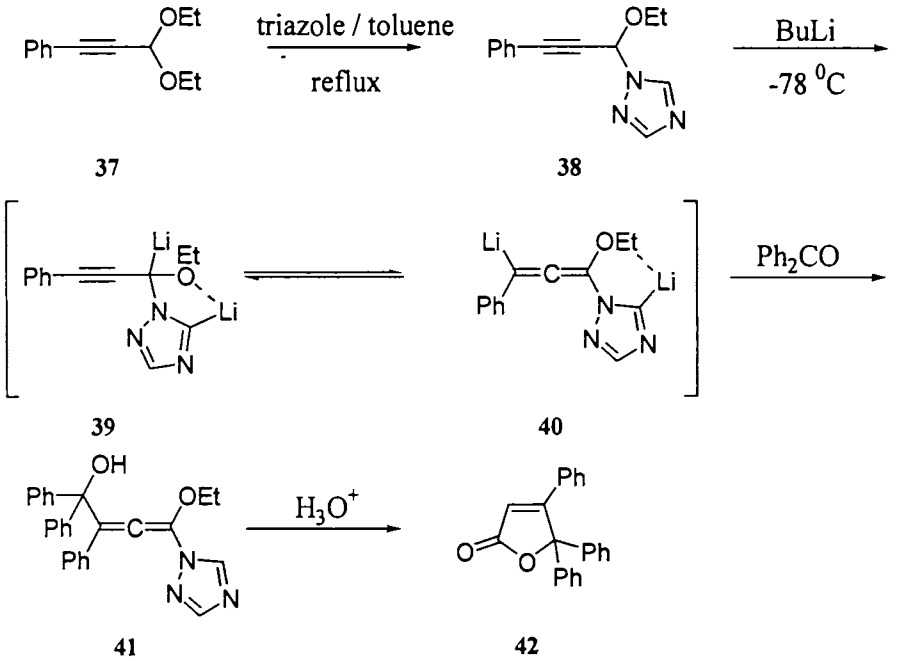


35 36

Scheme 13

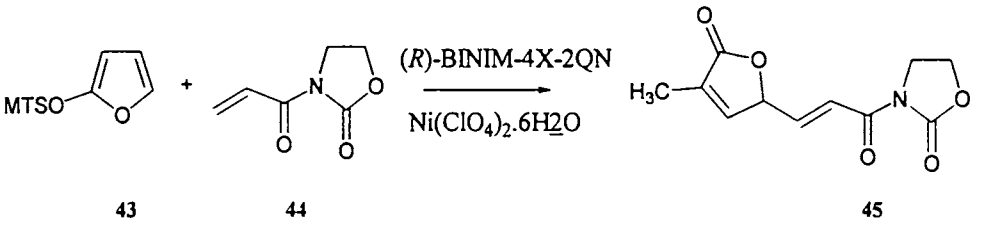
1.2.2.4. From Allenic Compounds. The first use of allenic compound for the lactone synthesis was reported by Ziegler and Sauermilch in 1930.[83] The usual procedure involves the reaction of appropriate allenic compounds with sulphuric acid, PCl_3, acetic anhydride and Br_2 in CCl_4 [84,85].

A novel synthesis of α,β-unsaturated γ-lactones via 1,2,4-triazole stabilized allenic anions was reported by Katritzky in 1997. The dianion of 1-(1,2,4-triazol-1-yl)phenylpropargyl ethyl ether **(38)** reacts with aldehydes and ketones to give 2(5H)-furanones.[86] (Scheme 14)



Scheme 14

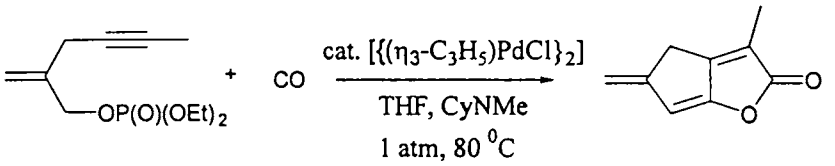
1.2.2.5. From Furan Derivatives. Furans are known to undergo photosensitized oxidation and ozonolysis to give 2(5H)-furanones.[4] Titanium silicate molecular sieves having MFI (TS-1) topology catalyses the oxidation of furans to corresponding furanones using dilute hydrogen peroxide as an oxidizing agent through the intermediacy of Oxygen.[87] Suga and co-workers reported the synthesis of chiral γ-butenolides from furan derivative via asymmetric Michael addition reaction. Chiral Ni(II) complexes, which are readily prepared from chiral BINIM-2QN or its derivatives and $Ni(ClO_4)_2.6H_2O$, were found to be efficient Lewis acid catalysts in the synthesis of chiral γ-butenolides from 2-silyloxyfurans and 3-alkenoyl-2-oxazolidinones resulting in high anti and enantioselectivities[88] (Scheme 15).



43 44 45

Scheme 15

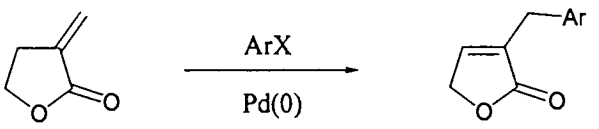
1.2.2.6. Metal Carbonyl Catalysed Reactions. Transition metal catalysed carbonylation is well-established route to synthesise 2(5H)-furanones. Commonly employed metals include Ni,[88] Pd,[89-91] Hg,[92] Ti,[93] Rd,[94] and Ru[95]. Acetylenic compounds undergo effective ring closure in presence of transition metal catalysts leading to the formation of corresponding 2(5H)-furanones. Highly unsaturated γ-lactones are synthesized by Pd-catalysed carbonylation of 2-(propargyl)allyl phosphates[96] (Scheme 16).



46 47 48

Scheme 16

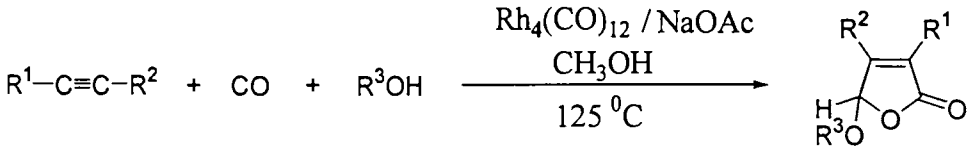
Arcadi *et al* in 2000 reported palladium catalysed arylation of the α-methylene-γ-butyrolactone leads to the formation of 2(5H)-furanones[97] (Scheme 17).



49 **50**

Scheme 17

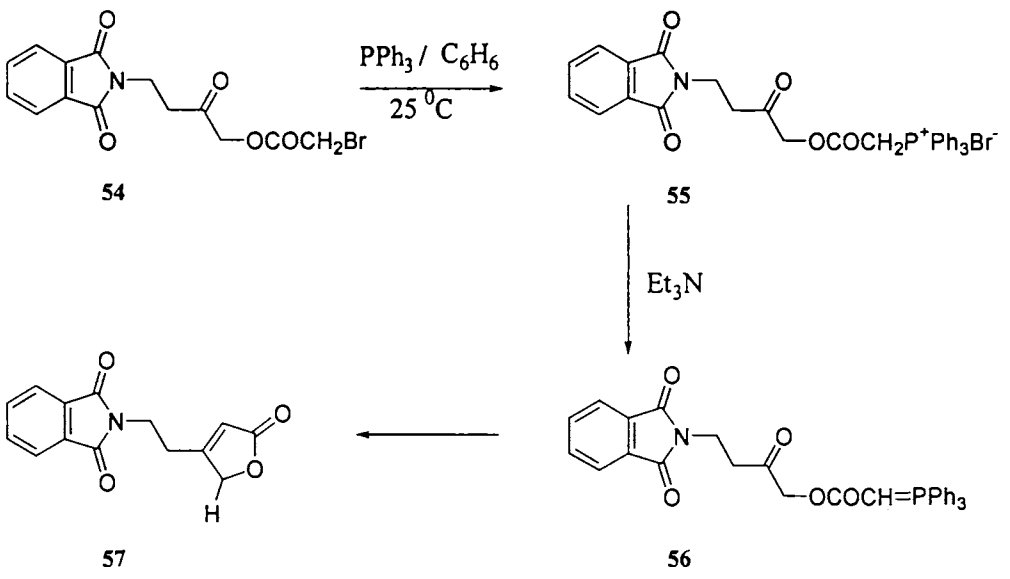
Rhodium catalysed synthesis of 5-alkoxy-2(5H)-furanones by the carbonylation of acetylenes in alcohol is reported by Mise *et al*[94] (Scheme 18).



51 **47** **52** **53**

Scheme 18

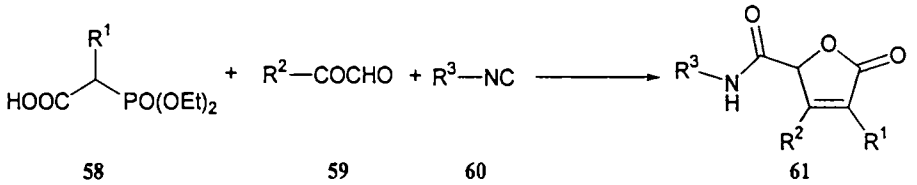
1.2.2.7. By Wittig Reaction. Wittig reaction is extensively employed in the synthesis of steroids containing 2(5H)-furanone ring systems.[98-103] In 1978 Krauser and Watterson employed this reaction as an efficient route to β-(2-phthalimidoethyl)-2(5H)-furanone in connection with the synthesis of alkaloid, cocculolidine.[104] (Scheme 19).



54 55 56 57

Scheme 19

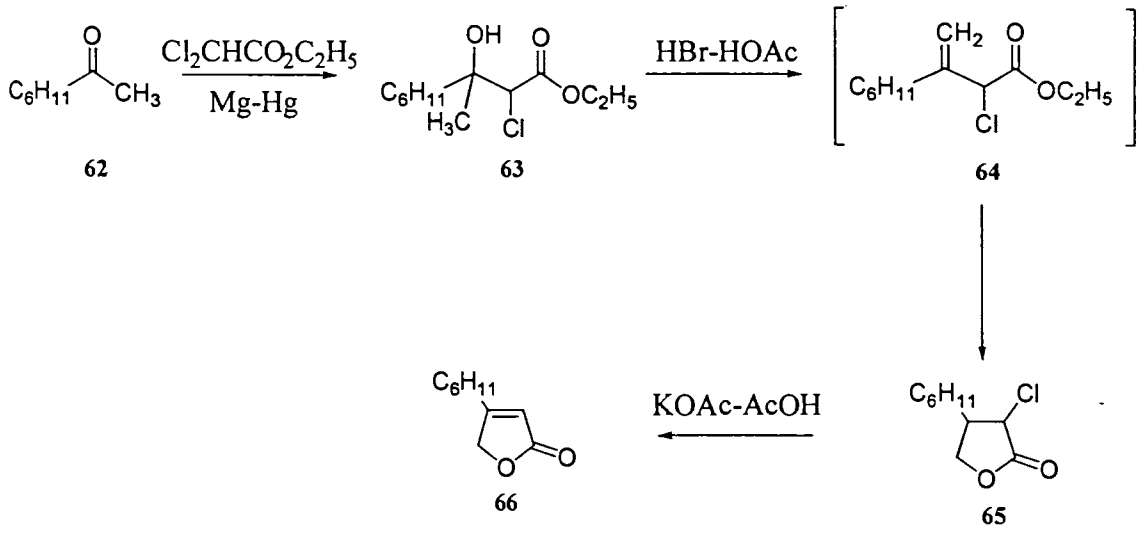
Synthesis of furanones by a novel one pot three component reaction followed by intramolecular Wittig-type reaction was reported by Beck *et al* in 2001. The total transformation is a combination of the Passerini three-component reaction involving isocyanides, arylglyoxals and a-substituted diethyl carboxylicmethanephosphonate followed by an intramolecular Wittig-type reaction[105] (Scheme 20).



58 59 60 61

Scheme 20

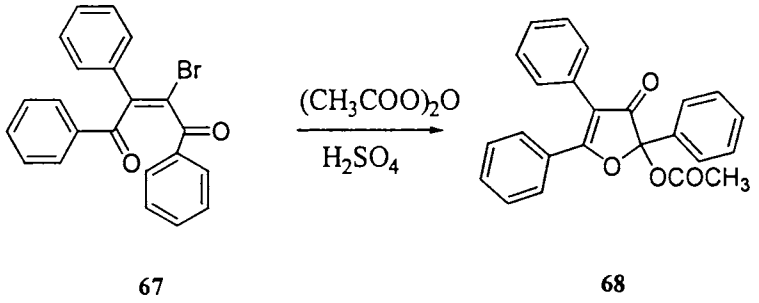
1.2.2.8. Darzen's-type Synthesis. A variation of the Darzens glycidic ester synthesis has also been successfully employed for the preparation of 2(5H)-furanones.[106,107] β-Cyclohexyl-2(5H)-furanone was prepared by this method (Scheme 21).



Scheme 21

1.2.3. Synthesis of 3(2H)-Furanones

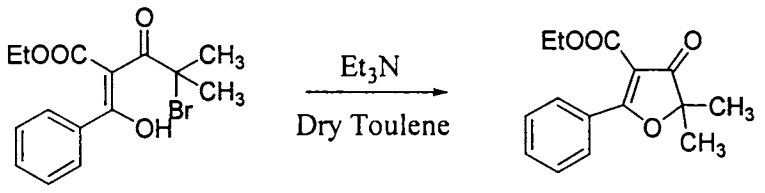
1.2.3.1. From Dibenzoylalkenes. 3(2H)-Furanones can be easily synthesized from dibenzoylalkenes. *Z*-bromodibenzoylstyrenes on addition-cyclisation reaction in presence of acidic reagents yield the corresponding 3(2H)-furanones.[108] Remarkable difference in reactivity is observed in the *E-Z* pair of dibenzoylstyrenes; only the "cis" isomer is converted to the corresponding furanone whereas the "trans" isomer failed to react under the same conditions (Scheme 22).



Scheme 22

1.2.3.2. From β-Ketoester. Another convenient method for the synthesis of 3(2H)-furanones involves cyclisation of α-haloacylketoesters.[109-113] Hydrolysis and decarboxylation of ethyl (α-bromoisobutyryl)-benzoylacetate (**69**), for

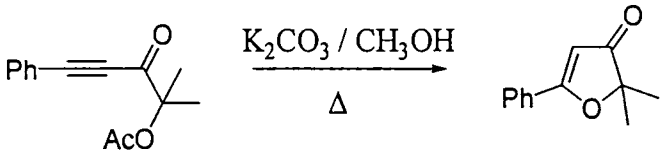
example, on treatment with triethylamine in dry toluene gave ethyl 4,5-dihydro-5,5-dimethyl-4-oxo-2-phenylfuran-3-carboxylate (**70**) in good yield (Scheme 23).



69 **70**

Scheme 23

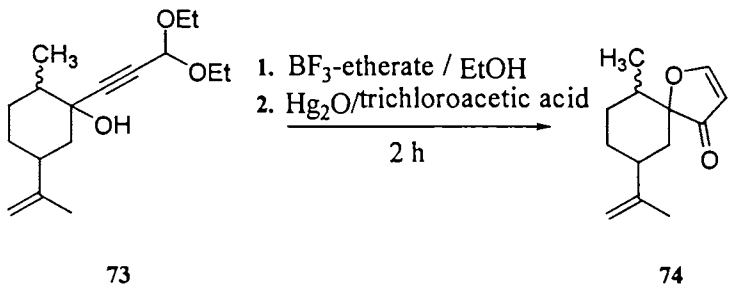
1.2.3.3. From Acetylenic Compounds. In 1984, Jackson *et al.* reported an alternative route for the synthesis of 3(2H)-furanones by the hydrolysis of corresponding readily accessible acetylenic ketones. [114] Acetylenic ketone **71** on heating under reflux with potassium carbonate in methanol yielded bullatenone (**72**) (Scheme 24).



71 **72**

Scheme 24

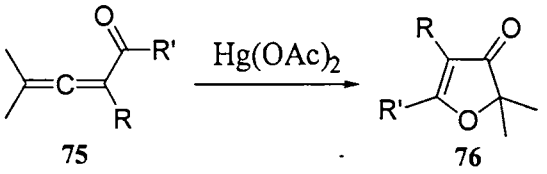
Reports of Williams *et al.* provides more information about the formation of 3(2H)-furanones from acetylenic precursors. Acetylenic alcohol **73** on reaction with boron trifluoride-etherate in absolute ethanol in the presence of catalytic amounts of mercuric oxide and trichloroacetic acid yielded spiro 3(2H)-furanone **74** in good yield.[115] (Scheme 25).



73 74

Scheme 25

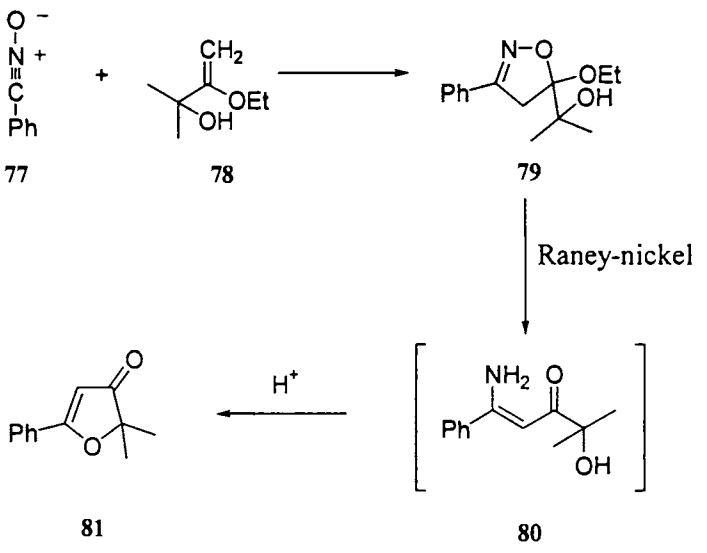
1.2.3.4. By Mercuric Acetate Oxidation. Wolff *et al.* have synthesized 3(2H)-furnanones by mercuric acetate oxidation of allenic ketones. [116] These results provide a simple conversion of readily accessible allenic ketones to 3(2H)-furanones (Scheme 26).



75 76

Scheme 26

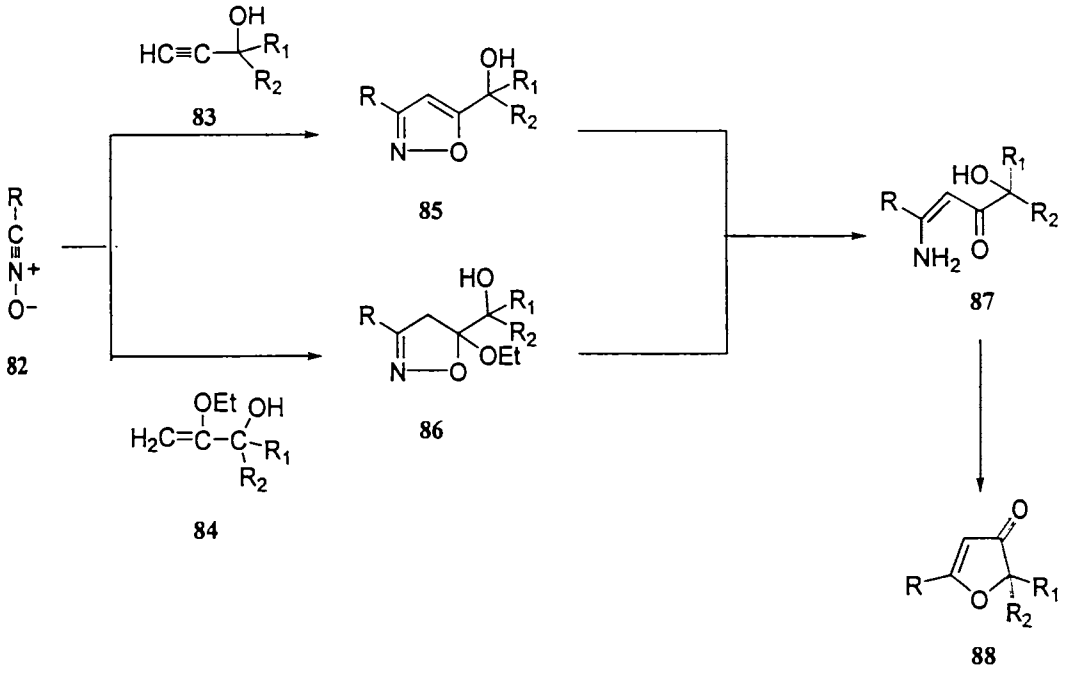
1.2.3.5. By Cycloaddition Followed by Reduction. Curran and co-workers have carried out extensive investigations on the synthesis of various 3(2H)-furnanones. They have developed a novel approach to the formation of aldol adducts such as **80** involving cycloaddition rather than carbonyl addition in the key carbon- carbon bond forming reaction. This strategy has been applied to develop a simple three-component route to substituted 3(2H)-furanones.[117] Cycloaddition of alcohol **78** and benzonitrile *N*-oxide **77** results in the formation of isoxazoline **79,** which on catalytic reduction yields 3(2H)-furanone **81** (Scheme 27).



77 78 79 80 81

Scheme 27

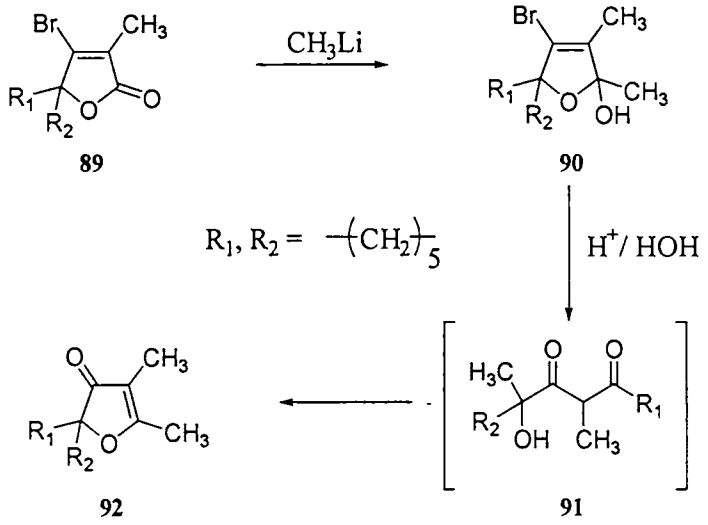
In yet another instant Baraldi *et al.* have reported a similar route to various substituted 3(2H)-furanones through cyclodehydration of γ-hydroxy-β-enaminoketones derived from 5-substituted-3-isoxazolemethanols [118] (Scheme 28).



82 83 84 85 86 87 88

Scheme 28

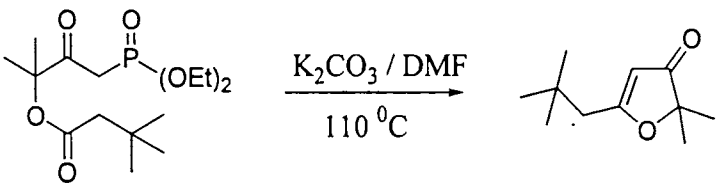
1.2.3.6. From γ-Hydroxy-β-dicarbonyl Systems. One of the general approaches for the synthesis 2,2-disubstituted 3(2H)-furanones involves the acid catalysed cyclisation of appropriate γ-hydroxy-β-dicarbonyl systems.[119] The synthetic sequence involves 1,2-addition of organometallic compounds to γ,γ'-disubstituted β-bromo-α,β-butenolides **89** followed by hydrolysis and acid catalysed cyclisation to the corresponding 3(2H)-furanone **92** via γ-hydroxy-β-dicarbonyl systems **91** (Scheme 29)



89 90 91 92

Scheme 29

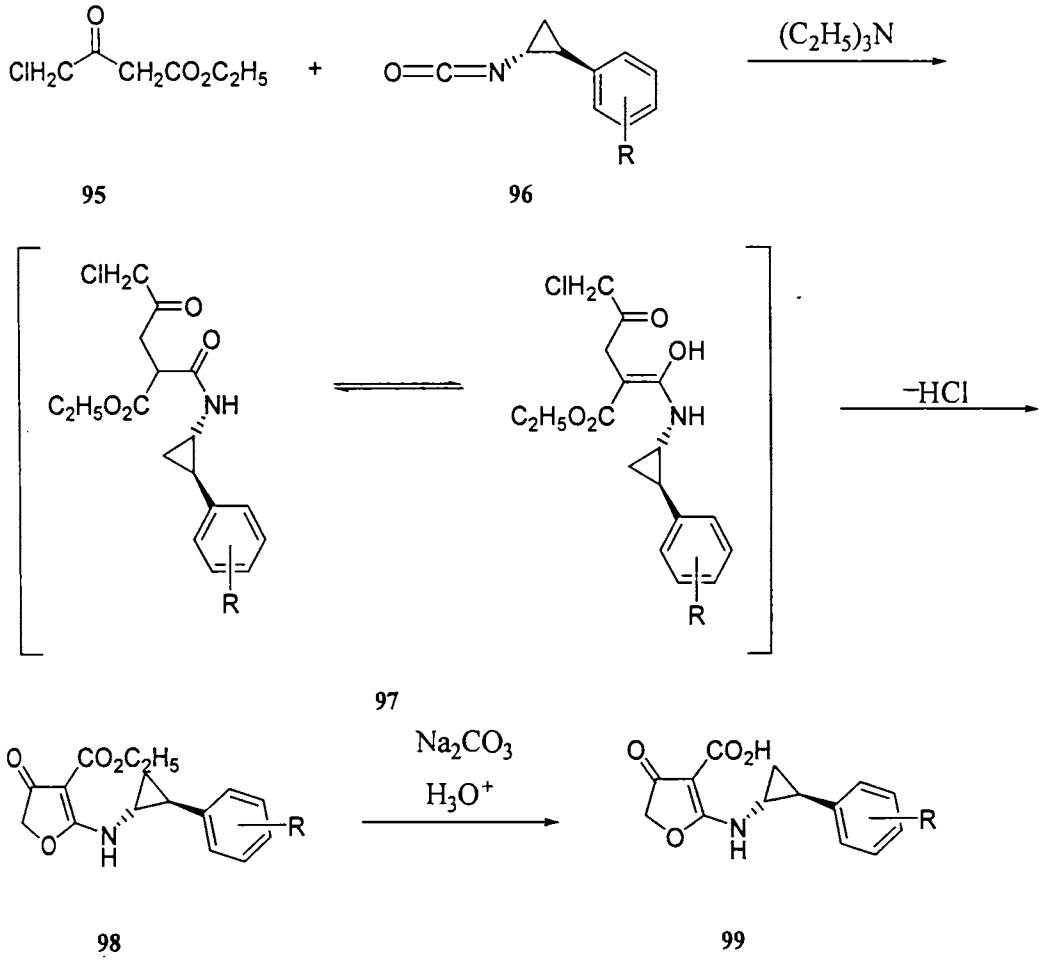
1.2.3.7. By Wadsworth-Emmons Condensation of γ-(Acyloxy)-β-ketophosphonates. Sampson and his group has provided a new route for the synthesis of 3(2H)-fruranone ring system.[120] γ-(Acyloxy)-β-ketophosphonates when treated with potassium carbonates undergo an intramolecular Wadsworth-Emmons type condensation to afford 3(2H)-fruranones (Scheme 30).



93 94

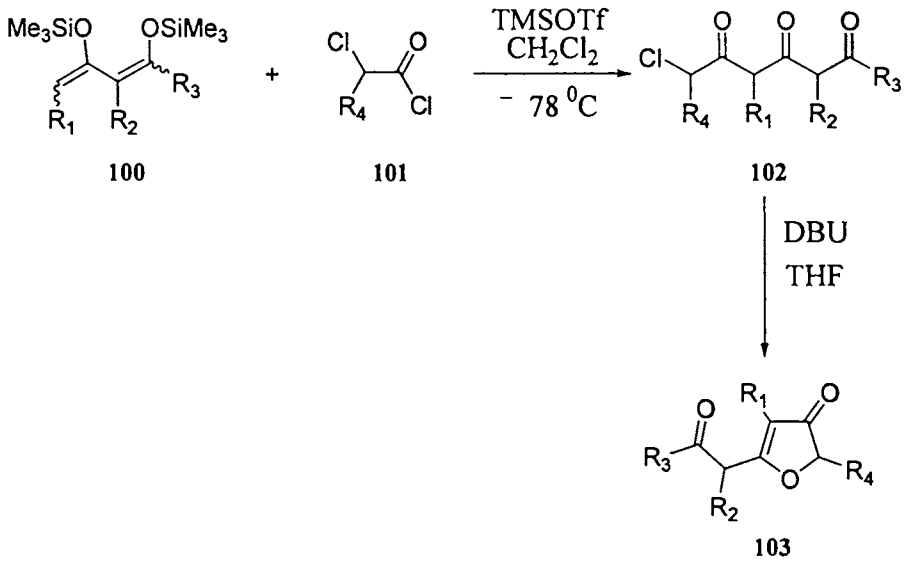
Scheme 30

1.2.3.8. By Capuano Fischer approach. A series of 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic acids was synthesised by Georgiev et al using the Capuano Fischer approach. The reaction involves base catalysed cyclocondensation which proceeds through the formation of a ketene intermediate and a C-O insertion into the furan ring to generate desired 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylate. Base catalysed hydrolysis of **98** results in **99**.[121] (Scheme 31).



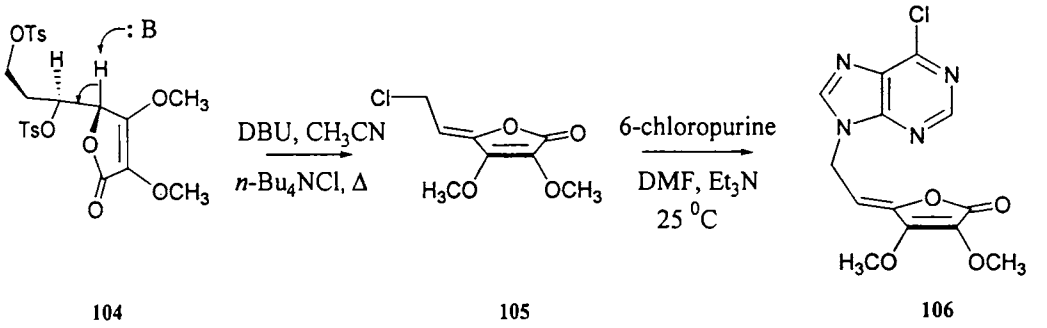
Scheme 31

1.2.3.9. Miscellaneous Methods. Chemo- and regio-selective synthesis of functionalised 3(2H)-furanones from bis(trimethylsiloxy)buta-1,3-dienes is reported by Langer and Krummel. Reaction involves the cyclisation reactions of 1,3-bis(trimethylsiloxy)buta-1,3-dienes with a-chlorocarboxylic acid chlorides.[122] (Scheme 32).



Scheme 32

Synthesis of purine derivatives of unsaturated lactones, which are antiviral as well as anticancer active is reported by Hakimelahi *et al* in 2001.[123] The reaction involves treatment of ditosylate **104** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *n*-Bu_4NCl in CH_3CN at reflux to produce corresponding (*Z*)-4-(2-chloroethylidene)-2,3-dimethoxybutenolides (**105**). The chloro compound **105** on condensation with 6-chloropurine in presence of Et_3N in DMF afford the corresponding N_9-alkylatedproduct **106** [123] (Scheme 33).



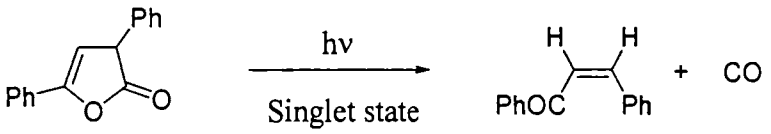
Scheme 33

1.3. Reactions of 2(3H)-and 2(5H)-Furanones

1.3.1. Photochemical Transformations

Light induced transformations of 2(3H)- and 2(5H)-furanones have been the subject of intensive study. Depending on the nature of the furanone ring and the substituents present, these compounds are known to undergo various interesting photochemical transformations. Some of the observed processes include decarbonylation,[124-127] decarboxylation,[128] solvent addition to double bonds,[129-132] aryl group migration,[132] and dimerisation.[133] Chapman and McIntosh have previously noted that a critical requirement for a clean photochemical cleavage of the acyl-oxygen bond is the presence of a double bond adjacent to the oxygen.[126] Stabilization of the incipient oxy radical was considered to be a determining factor in the photo cleavage of this bond. Product analysis based on steady-state irradiation and laser flash photolysis has been used to study the phototransformations of 2(3H)-furanones.

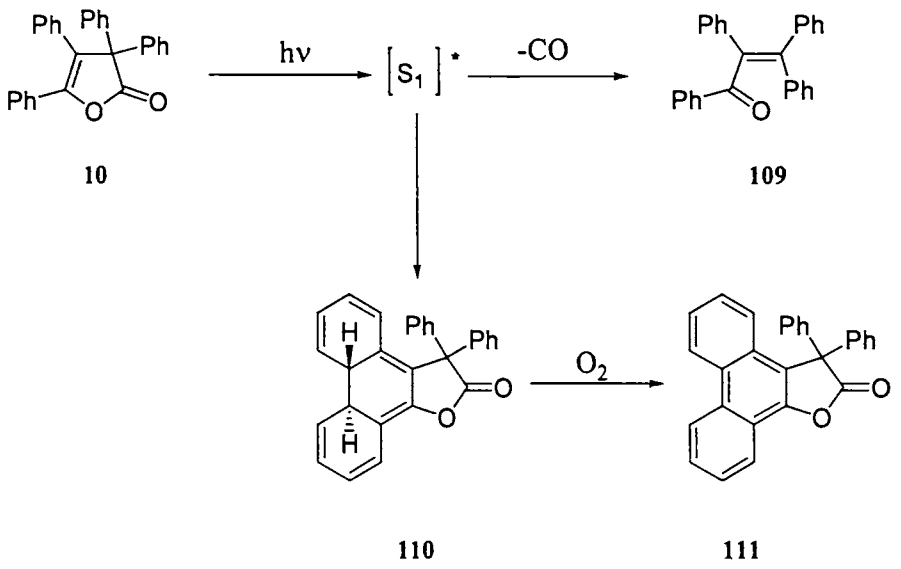
1.3.1.1. Photochemical Transformations of 2(3H)-Furanones. Observations on the light-induced transformations of the five-membered furanone ring system have shown that 2,5-diphenyl-2(3H)-Furanones undergo a facile decarbonylation when subjected to ultraviolet irradiation and produce α,β-unsaturated ketones as primary photoproducts[124-127,134] (Scheme 34).



107 **108** **47**

Scheme 34

Direct irradiation of a solution of the 3,3,4,5-tetraphenyl-2(3H)-furanone (**10**) in benzene or methanol gave a mixture of 3,3-diphenyl-phenanthro-[9,10-b]-furan-2(3H)-one (**111**) and 1,2,3,3-tetraphenylprop-2-en-1-one (**109**).[135] When irradiation was carried out in methanol saturated with oxygen the yield of cyclisation product was increased by 32% (Scheme 35).



10 109

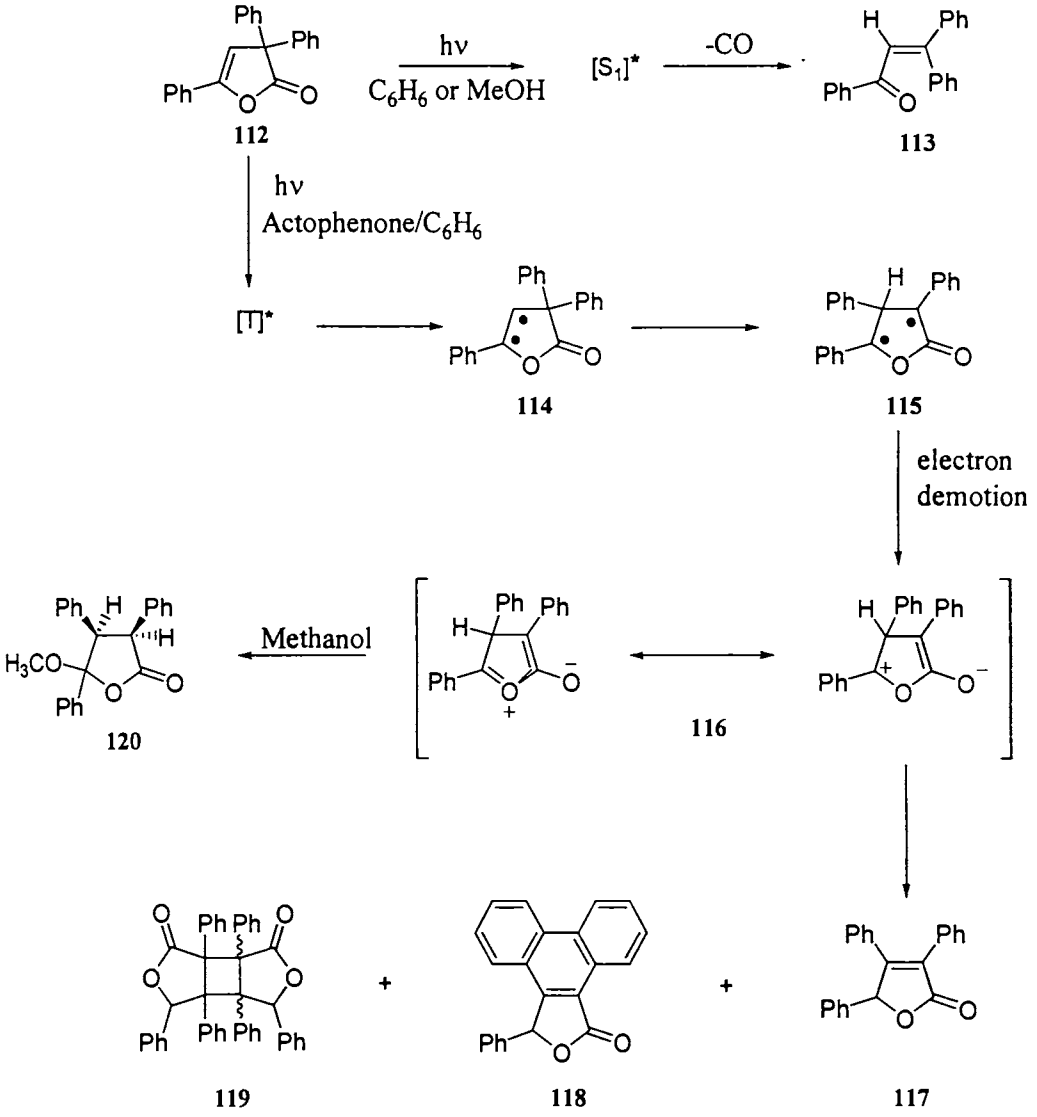
110 111

Scheme 35

Photolysis of a solution of 3,3,5-triphenyl-2(3H)-furnanone **(112)** in benzene or methanol also resulted in singlet-mediated decarbonylation to give the corresponding α,β-unsaturated carbonyl compound 1,3,3-triphenylpro-2-en-1-one **(113)**.[135] On the other hand, acetophenone-sensitized irradiation of **112** in benzene resulted in triplet mediated reaction leading to the formation of 3,4,5-triphenyl-2(5H)-furanone **(117)**, 5-phenanthro[9,10-c]-furan-2(5H)-one **(118)** and a dimeric product identified as **(119)** [135-137] Direct irradiation of **112** leads to the formation of 1,3,3-triphenylpropenone (**113**) by simple decarbonylation reaction.

The photochemical rearrangement of 2(3H)-furanones to give the corresponding 2(5H)-furanones and the subsequent formation of the phenanthrofuranone can be explained in terms of a pathway involving triplet-excited state.[136] In the triplet-excited state, which can be visualized in terms of a diradical structure, one of the C-3 aryl groups migrates through a bridged transition state to give the rearranged diradical intermediate **115**. Electron demotion in **115** will lead to a zwitterionic intermediate described by structure **116**. In presence of methanol, the zwitterionic intermediate is trapped to give 5-methoxy-3,4,5-triphenyl-2-furanone, **(120)**. In the absence of any protic solvents, the zwitterionic intermediate undergoes a hydride shift to give the rearranged 3,4,5-triphenyl-2(5H)-furanone **(117)**. This furanone, in turn, absorbs light and undergoes further

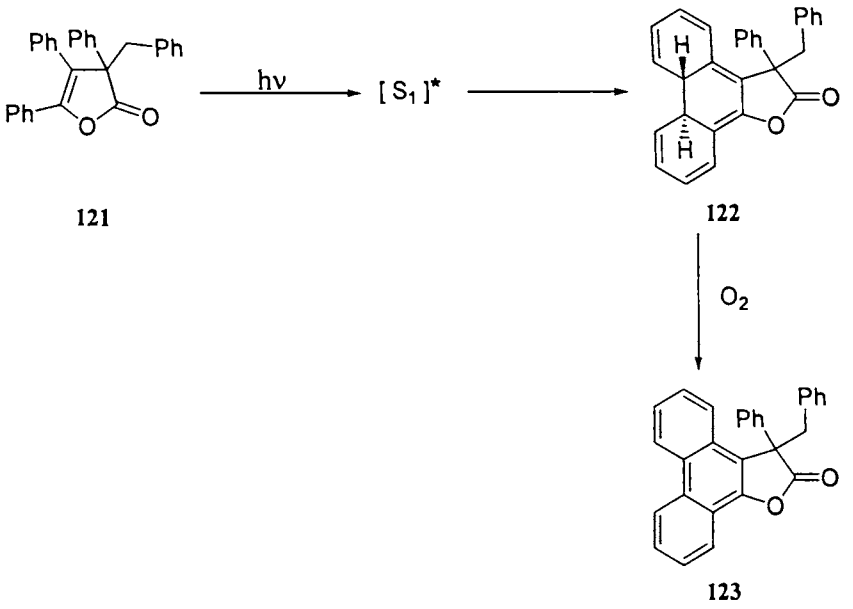
photocyclisation leading to dihydrophenanthrofuranone **(118)**. Alternatively, these 2(5H)-furanones can undergo photochemical (2+2) cycloaddition leading to the dimeric product **119** (Scheme 36).



Scheme 36

Photochemical transformation of 2(3H)-furanones containing a benzyl or benzoyl group at the 3-position has also been studied.[135] On direct irradiation in benzene and methanol, 3-benzyl-3,4,5-triphenyl-2(3H)-furanone **(121)** gave 3-benzyl-3-phenyl-phenanthro[9,10-b]furan-2(3H)-one **(123)** via dihydrophenanthrene intermediate **(122)** (Scheme 37). The presence of vicinal

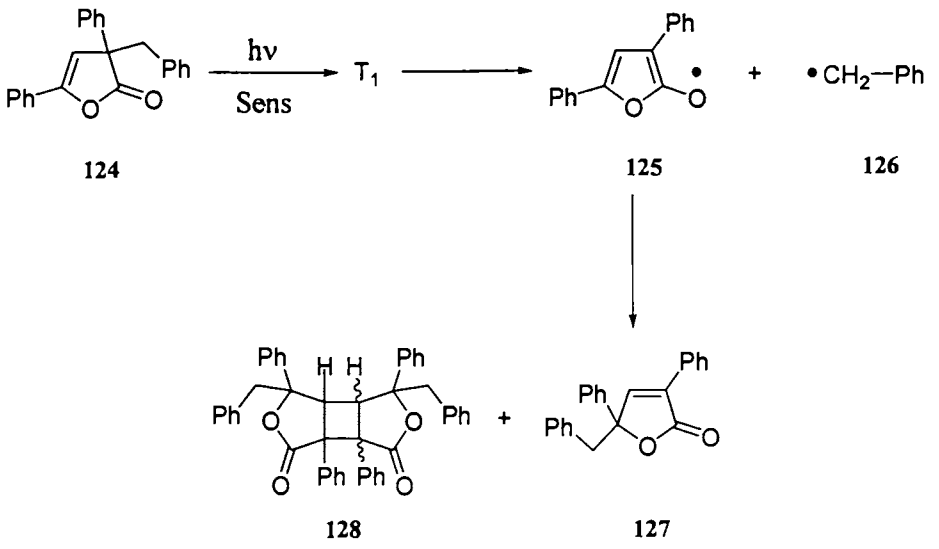
phenyl groups in the cis configuration by default at 4- and 5- position of furananones facilitates the formation of dihydrophenanthrenes.



121 122 123

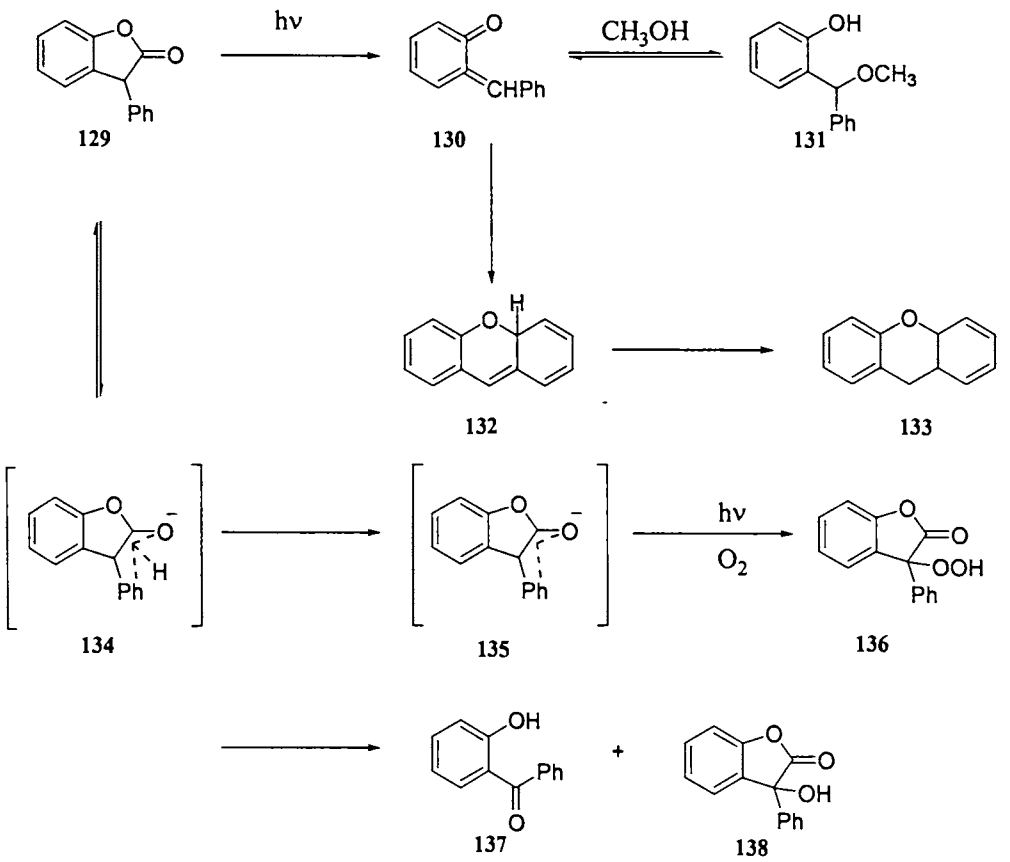
Scheme 37

Irradiation of the 3-benzyl-3,5-diphenyl-2(3H)-furnanone **(124)** in benzene solution using acetophenone as sensitiser gave a mixture of the rearranged lactone **127** and the bis lactone **128** along with a 25% recovery of the starting material. The triplet of **124** produced by excitation transfer from acetophenone triplet undergoes cleavage at the C-3 position to give benzyl and furanoxy radicals. The formation of the furanoxy radical was confirmed by laser flash photolysis studies.[138] Recombination of furanoxy and benzyl radicals leads to the formation of either the starting materials or the rearranged products (Scheme 38).



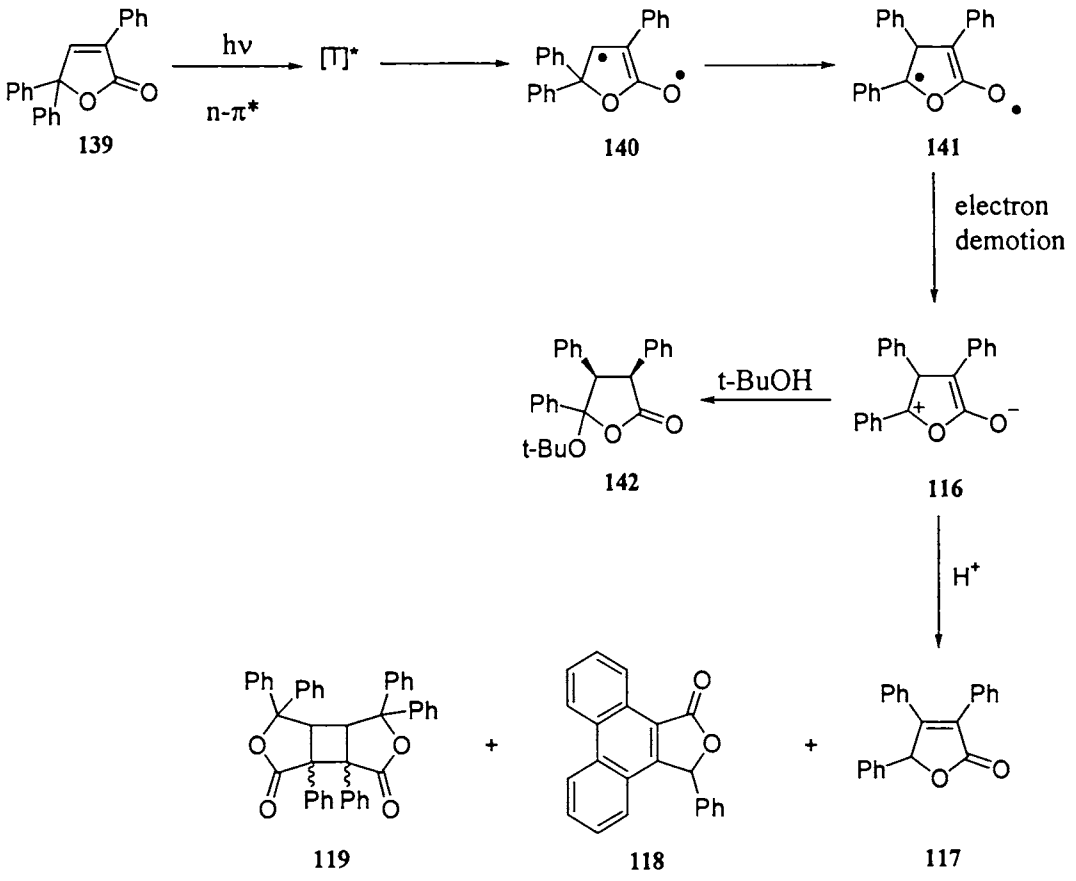
Scheme 38

Padwa and co-workers have shown that irradiation of benzo[b]-2(3H)-furanones **(129)** leads to a variety of products arising through quinonemethide intermediate **130** and through the excitation of the enolate ion **135** present in the solution.[139] The enolate ion in the excited state is attacked by the ground state oxygen to give α-hydroperoxylactone **136.** This transient intermediate is subsequently converted to compounds **137**and **138** (Scheme 39).



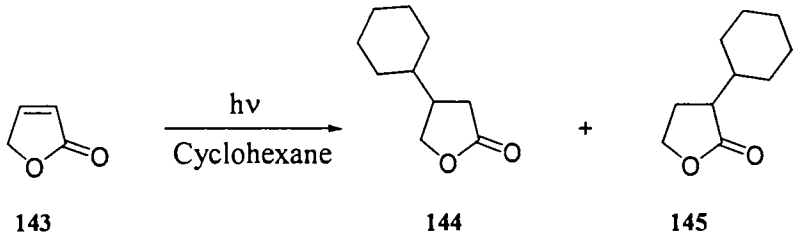
Scheme 39

1.3.1.2. Photochemical Transformations of 2(5H)-Furanones. 3,5,5-Triphenyl-2(5H)-furanone (**139**). on irradiation in benzene undergoes rearrangement from triplet state to yield 3,4,5-triphenyl-2(5H)-furanone (**117**) as the initial product. Longer irradiation in presence of molecular oxygen leads to the formation of dimer **119** and phenylphenanthro[9,10-c]furanone in high yield (**118**).[130-132] The reaction mechanism involved is shown in scheme 40. Here excitation is followed by an extremely efficient intersystem crossing to afford the n-π* triplet state. The bridging step and the subsequent cleavage leading to **141** are the first two steps of a di-π methane rearrangement. Electron demotion through divalent oxygen atom proceeds to give the zwitterionic intermediate **116**, which is trapped by the alcoholic solvent to give **142**. In the absence of a protic solvent the zwitterionic intermediate undergoes a hydride shift to give the observed product **117** (Scheme 40).



Scheme 40

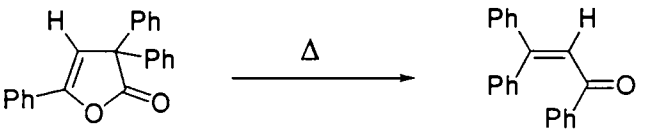
Toder *et al* [140] in 1977 observed that 2(5H)-furanone on irradiation in cyclohexane yields both α- and β-solvent adducts suggesting hydrogen abstraction by β-carbon (leading to α-adduct) and carbonyl oxygen (leading to β-adduct) of furanones in the excited state (Scheme 41).



Scheme 41

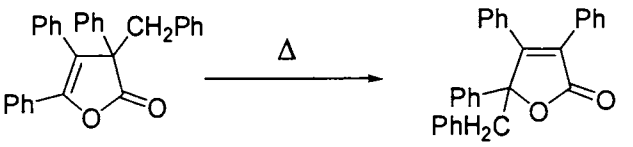
1.3.2. Thermal Transformations

In contrast to the photochemical transformation, the thermal transformations of 2(3H)-furnanones lead to decarbonylation products (Scheme 42) and, in some cases, rearrangement products, arising through a [1,3]-sigmatropic shift of the substituent groups[135] (Scheme 43).



112 113

Scheme 42

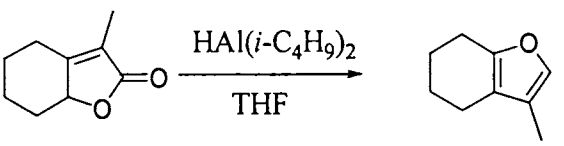


121 146

Scheme 43

1.3.3. Conversion to Furan Derivatives

Minato and Nagasaki have reported an elegant method for the conversion of 2(5H)-furanones to furans.[141] Their method consists of adding diisobutylaluminium hydride (DIBAL-H) in tetrahydrofuran to a solution of the lactone. The following is an example of the application of this method[142] (Scheme 44).

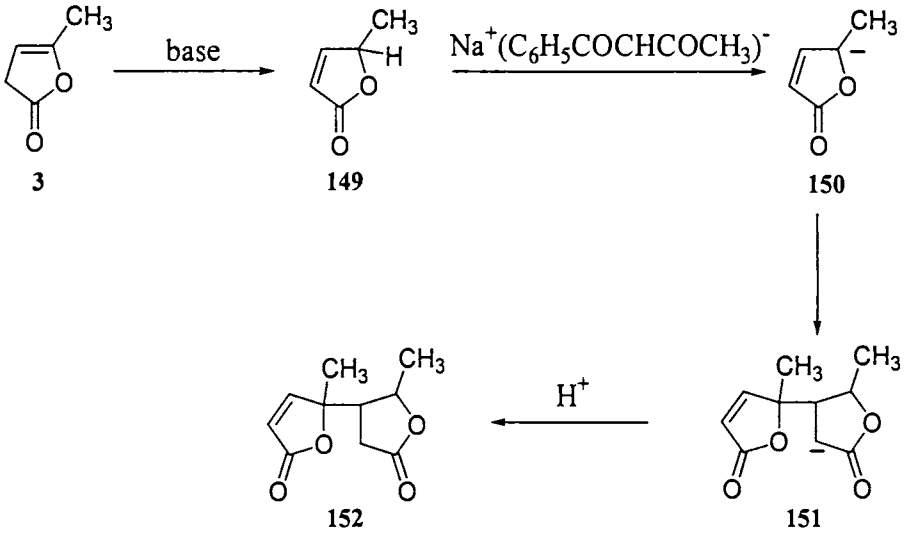


147 148

Scheme 44

1.3.4. Dimerisation

The α– and β–isomers of angelicalactone or a mixture of the two, forms dimers on heating in presence of a catalyst such as 3° amines, alkali metal alkoxides, sodium salt of benzoylacetone, anhydrous potassium carbonate, alkali metal hydroxides and free alkali metals.[143-145] On reaction with anhydrous potassium carbonate, both α– and β–angelicalactone gave the same dimer. It was suggested that α-lactone **3** isomerises in presence of a base to the β–lactone **149**, which then dimerises via its anion intermediate **150**. The following mechanism was suggested (Scheme 45).



Scheme 45

1.3.5. Polymerisation

2(5H)-furanone was found to be a poor monomer.[146] α–Angelicalactone when treated with BF_3 in CS_2 undergoes step-growth polymerisation rather than a chain-growth mechanism usually encountered in vinyl polymerisation. The polymer possessed a head to tail structure and is represented as shown below (Figure 4).

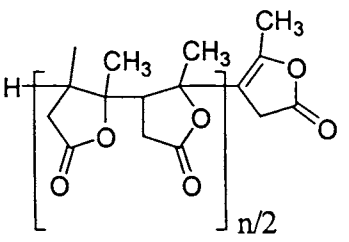
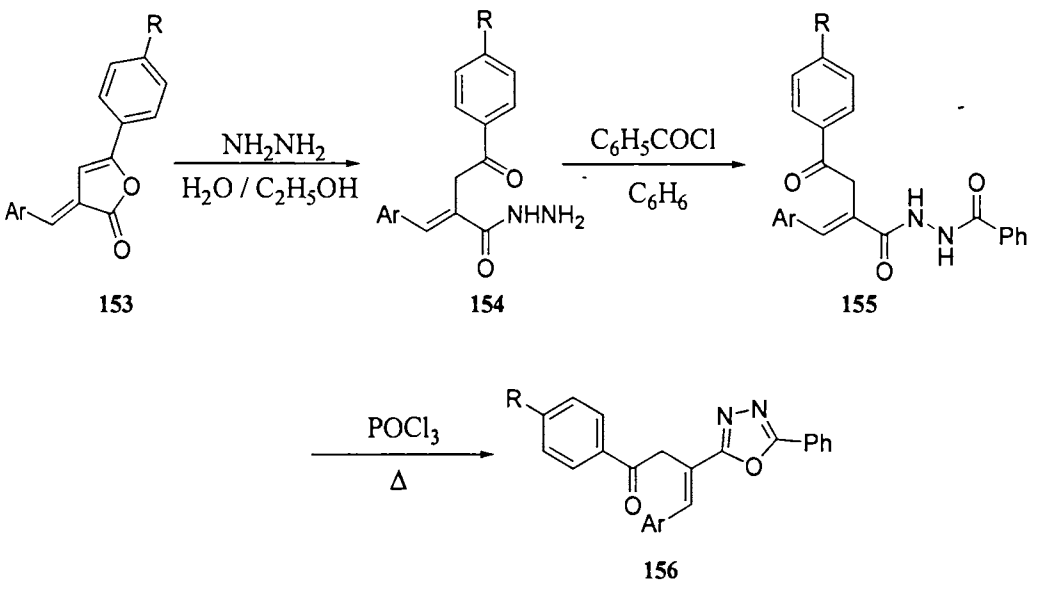


Figure 4

1.3.6. Conversion of 2(3H)-Furanones into 1,3,4-Oxadiazoles

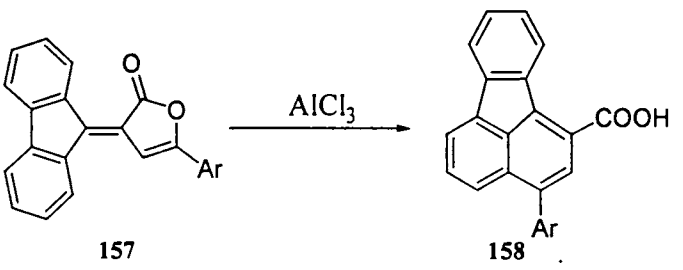
A series of biologically important 1,3,4-oxadiazoles[147] were synthesized from corresponding 2(3H)-furanones through cyclodehydration by Abdel-Sattar and coworkers in 2003 (Scheme 46).



Scheme 46

1.3.7. Reaction under Friedel-Craft's Condition

Filler and Leipold synthesized a series of substituted napthoic acids by the reaction of α-arylidene-γ-phenyl-2(3H)-furanones.[148] This type of ring closure has been effected on 9-fluorenylidene butenolides to give fluoranthenecarboxylic acids (Scheme 47).



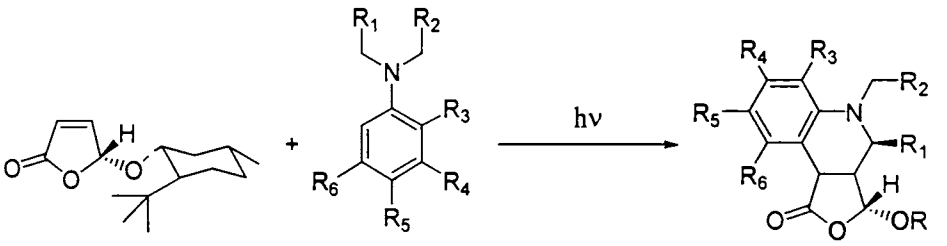
157 158

Ar = C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$

Scheme 47

1.3.8. Radical-Tandem Reactions with Aniline Derivatives

Samuel *et al* reported an efficient and stereoselective radical-tandem reaction of simple alkyl derivatives of aniline to a chiral furanones initiated by photochemically induced electron transfer to yield corresponding 1,2,3,4-tetrahydroquinolines[149] (Scheme 48).

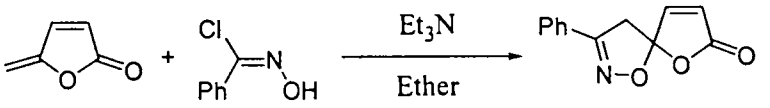


159 160 161

Scheme 48

1.3.9. 1,3-Dipolar Cycloaddition Reaction with Nitriloxide

5-Methelene-2(5)-furanones(**162**) are reported[150] undergoes 1,3-dipolar cycloadditions with 4-substituted aryl nitriloxides to give corresponding spiroisoxazolines. **162** on reaction with phenyl nitriloxides inpresence of hydroquinone and triethyl amine yields corresponding 3,3-diaryl-3a,6a-dihydro-4-oxospiro[isoxazolino-5',6-isoxazole[3,4-c]furanone] (Scheme 49).

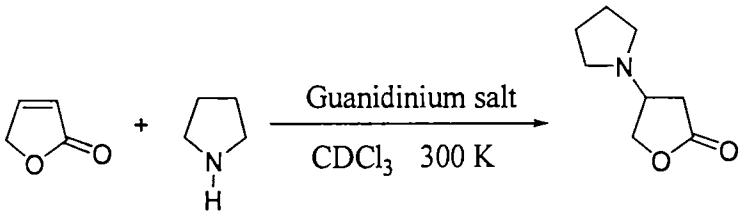


162 163 164

Scheme 49

1.3.10. Conjugate Addition with Amines

2(5)-Furanones are known to undergo Michael addition with certain amines to yield β-aminolactones. Alcazar and coworkers[151] in 1995 reported such a conjugate addition of pyrrolidine to 2(5)-furanones in the presence of bicyclic guanidinium salt catalyst by selective hydrogen bond stabilization of the transition state. From the synthetic point of view this conjugate addition yielding β-aminolactones is of considerable interest, allowing flexible and enatioselective routes to β-lactams.[152] (Scheme 50)

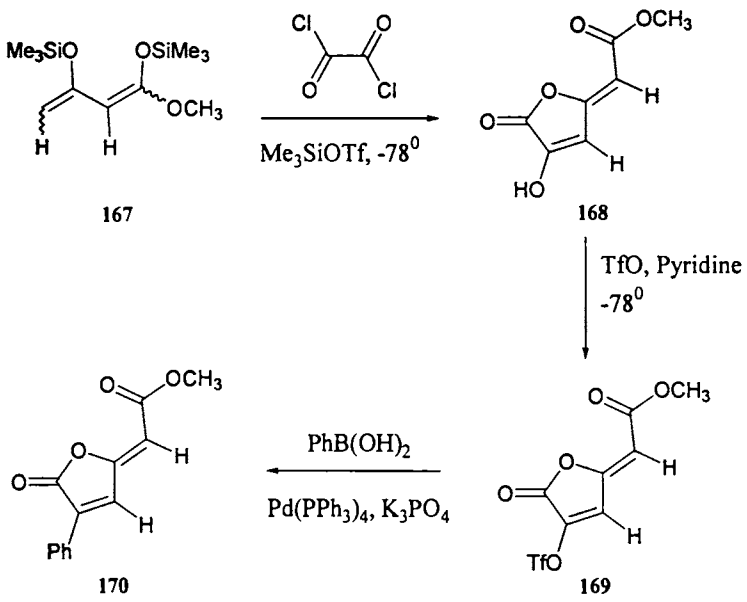


151 165 166

Scheme 50

1.3.11. Suzuki Cross-Coupling Reactions of γ-Alkylidene-2(5H)-Furanones

α-Hydroxy- γ-alkylidene-2(5H)-furanones were efficiently functionalised by Suzuki Cross-coupling reactions via the corresponding enol triflates. The natural product vulpinic acid (**170**) is prepared by this methodology.[153] (Scheme 51)



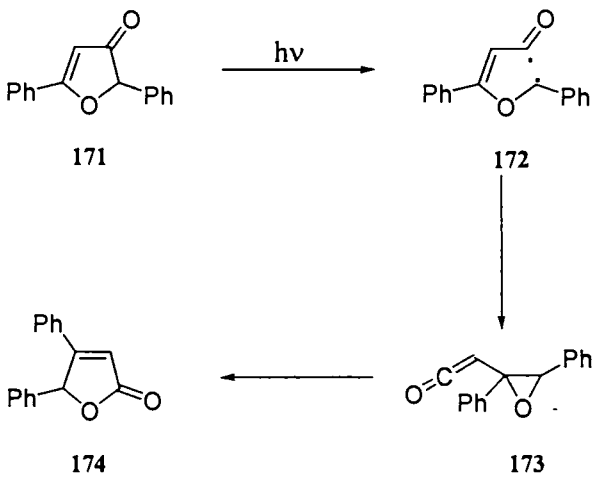
Scheme 51

1.4. Reactions of 3(2H)-Furanones

Unlike unsaturated γ-lactones, chemistry of 3(2H)-furanones has been less extensively explored. However, a few significant reports on the photochemistry and biological activity of 3(2H)-furanones are available in literature. In the following section, a brief discussion of the chemistry and biochemistry of 3(2H)-furanones is presented.

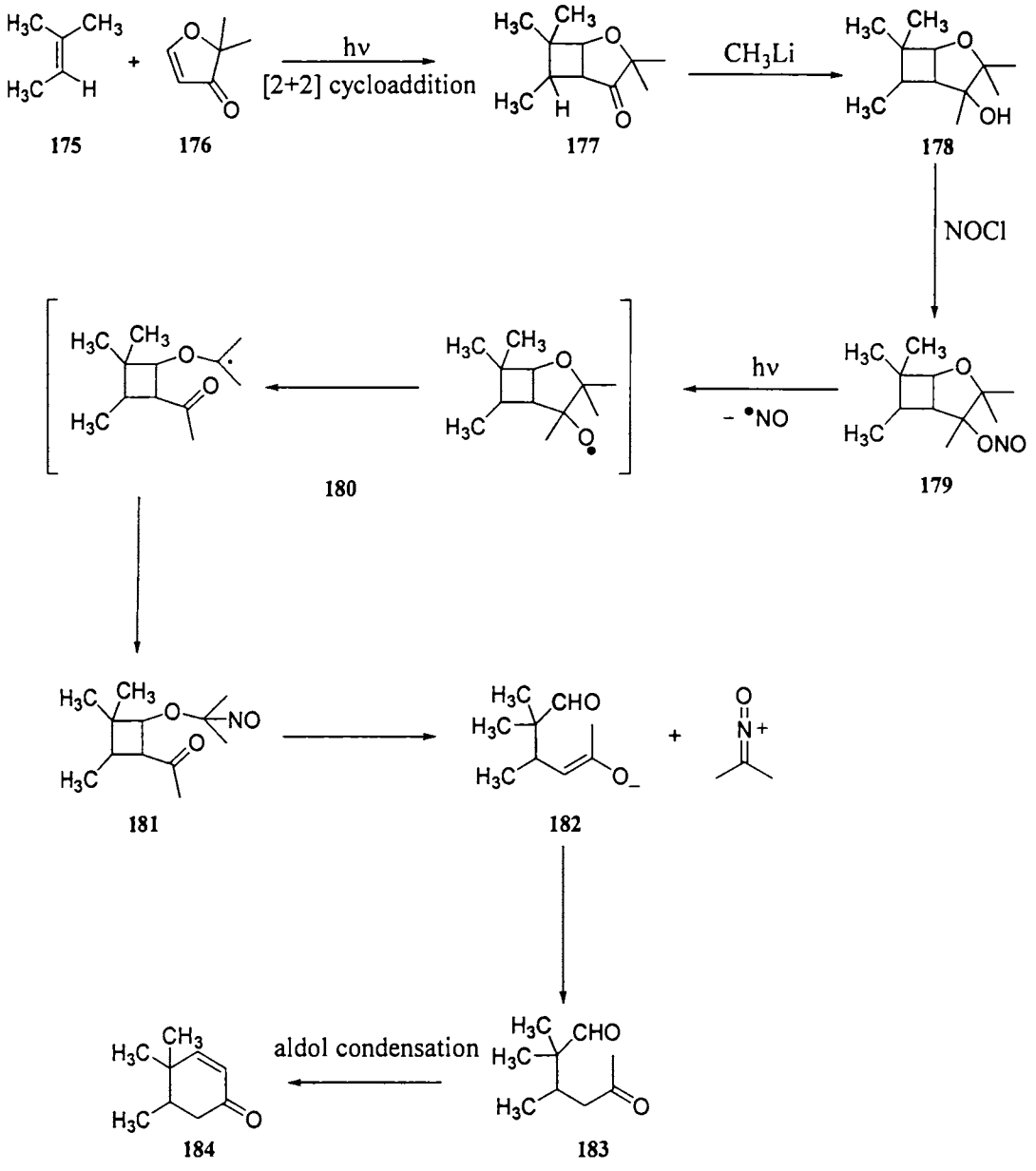
1.4.1. Photochemical Transformations

Padwa and co-workers in 1976 reported a novel rearrangement, which occurs upon irradiation of 2,5-diphenyl-3(2H)-furanone **(171)** and described some of the salient features of this reaction.[154] Irradiation of **171** in benzene under argon atmosphere yielded 4,5-diphenyl-2(5H)-furanone **(174)** in high yield. An attractive pathway for the formation of **174** involves initial homolytic cleavage of the bond α- to the carbonyl group to give a 1,5-diradical **(172)**. Subsequent rearrangement of this species to a 1,3-diradical followed by ring closure would yield an epoxy ketene **173**, which rearrange to **174** (Scheme 52).



Scheme 52

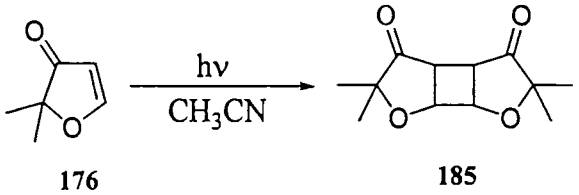
Baldwin *et al* has reported photo induced intermolecular cycloaddition reaction of various 3(2H)-furnaones.[155-157] The furanone/alkene cycloaddion reaction present an interesting and novel pathway to cyclohexanones.[158] The high material yields and regiochemcial preferences of the photoaddition step when combined with the overall ease and efficiency of the fragmentation/cyclodehydration process render the reaction sequences a general annelation technique. It involves the oxidative fragmentation of C_2-C_3 bond of **179** by virtue of the considerable stability of the radical **180** (Scheme 53).



175 176 177 178 179 180 181 182 183 184

Scheme 53

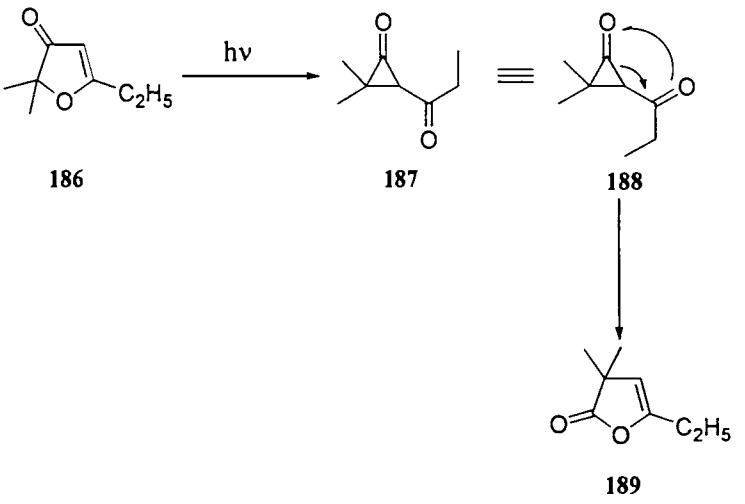
In the absence of alkenes, 3(2H)-furanones in acetonitrile undergoes photodimerisation[159] (Scheme 54).



176 185

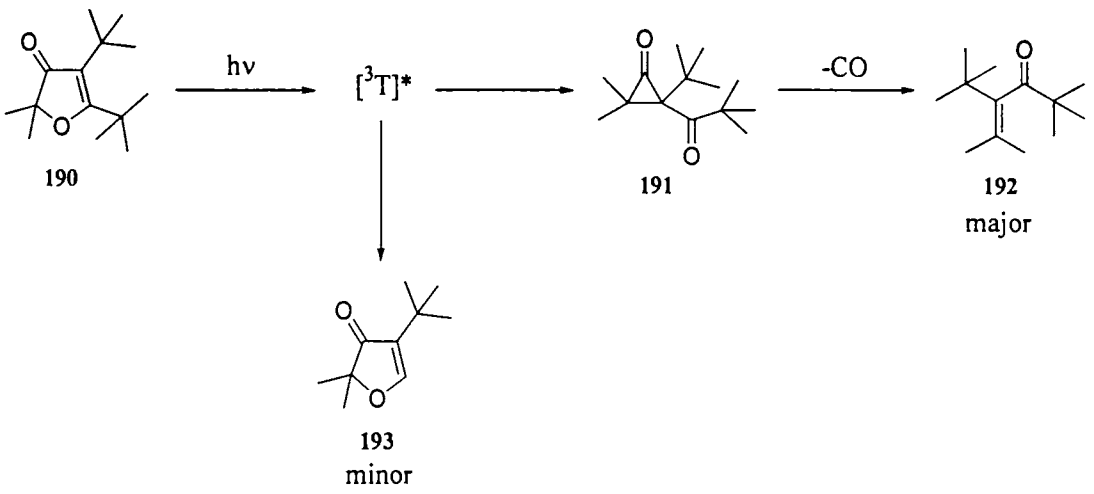
Scheme 54

On irradiation, alkyl-substituted 3(2H)-furanone **186** rearranged to the corresponding 2(3H)-furanone, **189**[160]. The mechanism involves the formal cyclopentene-vinylcyclopropane rearrangement of **186** to **187** followed by the reverse process with involvement of the other cyclopropane center to yield **189**. While this reaction mechanism is reasonable and consistent with mechanistic suggestions for other similar photochemical reactions, there is no direct evidence supporting the intermediacy of acylcyclopropanones **187** in the rearrangement (Scheme 55).



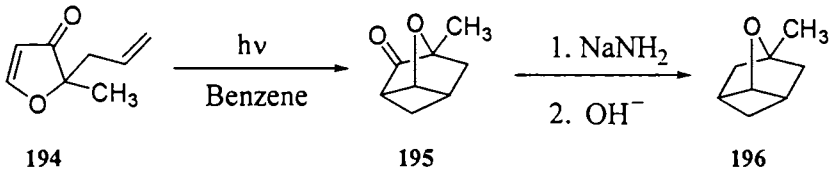
Scheme 55

Highly-crowded 2,2-dimethyl-4,5-di-*tert*-butyl-3(2H)-furanone **(190)** on the other hand gave the decarbonylated product **192** as major and 2,2-dimethyl-4-*tert*-butyl-3(2H)-furanone **193** as minor product on irradiation in benzene (Scheme 56). The mechanism involves the rearrangement of the furanone to an acylcyclopropanone followed by decarbonylation to yield **192**. This unique observation is due to the nonbonded strain energy of **190**, which is released on conversion to **191** and its rotation about acyl-cyclopropyl bond. Mechanism leading to **193** is less obvious. Direct γ-cleavage and disproportionation to isobutylene and **193** could be the simplest rationalization.



Scheme 56

Margaretha and co-workers have reported the light-induced regioselective intramolecular [2+2] photocycloaddition reactions of 2-methyl-2-(alk-2-enyl)-3(2H)-furanone (**194**).[161] Irradiation of **194** resulted in the cycloaddition to terminal alkene with a high degree of regioselectivity where always only one orientation of addition of the exocyclic double bond to the C=O bond was observed (Scheme.57).

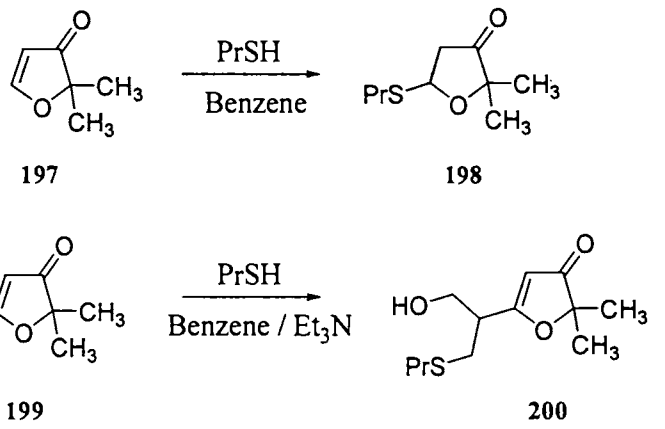


Scheme 57

1.4.2. Conjugate Addition Reactions

Kupchan [162] and Le Quesne [163] have independently reported the conjugate addition of terpeniods like jatrophone and eremantholide with propanethiol to yield monoadducts. Later on, reports of Smith *et al* in 1981 revealed an adaptable procedure involving conjugate addition which would permit cross linking, a process that has been suggested to enhance activity of many antitumor agents.[164] Studies on the reactivity of several 3(2H)-furanones with excess propanethiol employing acidic, neutral and basic reaction conditions showed the predominance

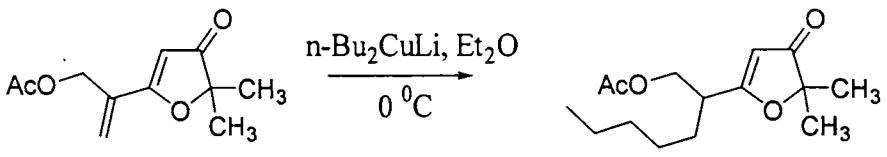
of a free radical induced addition of propanethiol under neutral conditions and a polar addition under acidic and basic regimes (Scheme 58).



197 198 199 200

Scheme 58

They have observed furadienone which possesses a good leaving group on the δ'-carbon, when treated with excess lithium di-*n*-butylcuprate yielded furanone through δ,δ'-conjugate addition (Scheme 59).

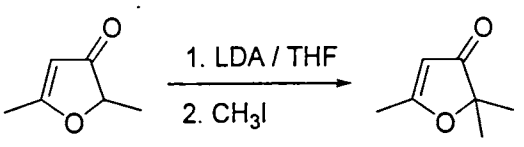


201 202

Scheme 59

1.4.3. Alkylation Reactions

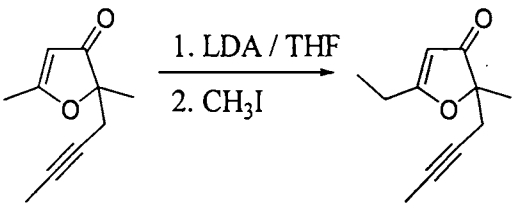
Smith *et al* in 1981 studied the alkylation reactions of 3(2H)-furanone ring system.[164] Treatment of lithium enolate of 2,5-dimethyl-3(2H)-furanone with alkyl halides resulted in exclusive alkylation at the α'-position (Scheme 60).



203 204

Scheme 60

On the other hand, reaction of α',α'-disubstituted derivatives of these furanones afforded excellent yield of γ-alkylated product (Scheme 61). The reactivity of these furanones found to be not affected by the degree of either α or γ-substituent. Based on the observations, in those cases where the dienolate incorporates an exocyclic double bond, γ-alkylation is the preferred mode. Conversely, dienolates possessing an endocyclic olefin yield exclusively α-adducts



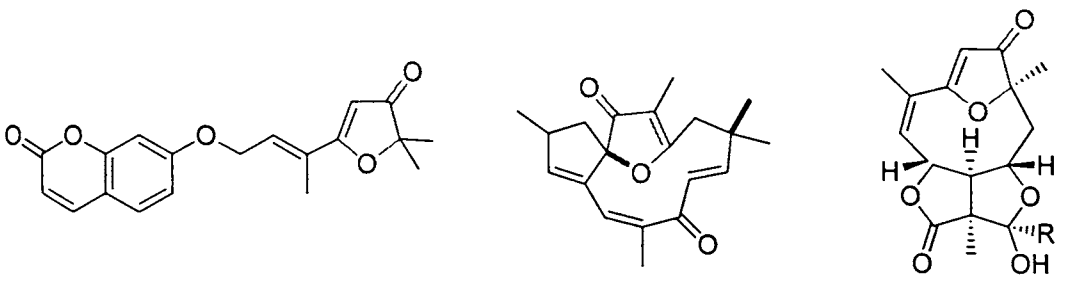
205 **206**

Scheme 61

1.5. Biological Activity

The synthesis and reactions of simple derivatives of 2(3H)- and 3(2H)-furanones have attracted considerable attention in recent years, primarily in connection with development of routes to antitumor agents that contain this ring as central structural unit.

In the light of enormous interest in the inhibition of neoplastic activity[165] by many guianolides and pseudoguianolides as well as antitumor activity of terpenes containing the 3(2H)-furanone components such as jatrophone,[166] geiparvarin,[167] the eramantholides [168] and tirotundin,[169] numerous synthetic efforts have been directed towards these substances.



Geiparvin Jatrophone Eremantholide

R = i-Pr

Figure 5

1.6. Outline of the Research Problem and its Importance

Synthesis and transformations of 2(3H)-furanones have been the subject of intensive study. These compounds are known to undergo various interesting thermal and photochemical transformations such as decarbonylation, decarboxylation, solvent addition to double bonds, migration of aryl substituents and dimerisation. 3,3,5-Triphenyl-2(3H)-furnanone on direct irradiation undergoes singlet mediated decarbonylation to yield an α,β-unsaturated carbonyl compound. On the other hand, sensitized irradiation of 3,3,5-triphenyl-2(3H)-furnanone resulted 1,2-phenyl migration leading to 2,4,5-triphenyl-2(5H)-furanone along with corresponding phenanthrofuranone. Most of the investigations on 2(3H)- and 2(5H)-furanones were intended at understanding the nature of the excited states involved in the observed transformation and the role of substituents at the 3- and 5-positions of the furanone ring system in controlling the course of the photochemical pathways followed by these molecules. Hence we propose to synthesis few aryl-substituted 2(3H)-furanones to study the effect of nature of substituents at the 3- and 5-positions of the furanone ring system on the course of their photochemical transformations.

Our interest in the synthesis of various 3(2H)-furanones is three fold: (1) Selection of the above synthetic target demanded the development of an efficient and potentially general strategy for the construction of 3(2H)-furanone ring, (2) chemistry of this increasingly important heterocycle has not received due attention,

(3) it appeared that simple 3(2H)-furanones would be ideal substrate to model the mode of biological action of antitumor agents which possess this structural element.

1.7. Objectives

1. To synthesise few 2(3H)-furanones having triaryl substituents at 3- and 5-positions.

2. To synthesise a few 2(3H)-furanones incorporating heteroaromatics from the corresponding dibenzoylalkene-type systems.

3. To synthesise various 2-substituted 3(2H)-furanones

4. To study singlet and triplet mediated transformations of a few representative 2(3H)-furanones synthesized by us and to analysis the effect of substituents at 3 and 5 positions on the course of their reaction.

5. To explore the thermal and photochemical transformations of 3(2H)-furanones.

6. To assess the biological activity of various 3(2H)-furanones.

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Chapter 2

SYNTHESIS OF 5-ARYL-3,3-BIS(4-CHLOROPHENYL)-3H-FURAN-2-ONES

Base-catalysed condensation of 4,4'-dichlorobenzil with suitably substituted acetophenones results in the formation of corresponding dibenzoylstyrenes. Under the influence of heat, these dibenzoylstyrenes rearrange to give the corresponding 2(3H)-furanones. In this chapter, we describe our endeavours on the synthesis and characterisation of several 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones.

2.1. Introduction

2(3H)-furanones are known to undergo various interesting photochemical and thermal transformations.[1] The observed process include decarbonylation,[2,3] decarboxylation,[4] solvent addition to double bonds,[5] aryl group migration,[6] and dimerisation.[7] Most of the investigations on 2(3H)-furanones were intended at understanding the nature of the excited states involved in the observed transformation and the role of substituents at the 3, 4, and 5-positions of the furanone ring system in controlling the course of the photochemical pathways followed by these molecules. Thus, it has been established that the decarbonylation reaction is singlet mediated while aryl group migration, dimerisation and solvent addition reactions are triplet mediated.[1a,b] Furthermore, ionic intermediates have been proposed to account for the observed aryl group migration.[2] In order to understand the mechanism of aryl group migration, the influence of the nature of the aryl group present on the 5-position was investigated in detail.[2] Though the migratory aptitude of different aryl groups present at the 3-position has been investigated in some detail, no attempt has hitherto been made on assessing the influence of the nature of aryl groups present at the 3-position in controlling the reactivity of 2(3H)-furanone.[1b] Since ionic intermediates are involved in aryl group migration, we reasoned that the nature of the aryl groups

present at 3-position would have a profound effect on the major reaction pathway followed by these molecules. In this context, we attempted to explore the effect of the nature of aryl groups present at the 3-position in controlling reactivity of 2(3H)-furanones.

A convenient method for the synthesis of 3,3,4-triaryl-2(3H)-furanones is by the thermolysis of corresponding dibenzoylstyrene precursors.[9-11] We adapted this procedure for the synthesis of a few 5-aryl-3,3-bis(4-chlorophenyl)-2(3H)-furanones.

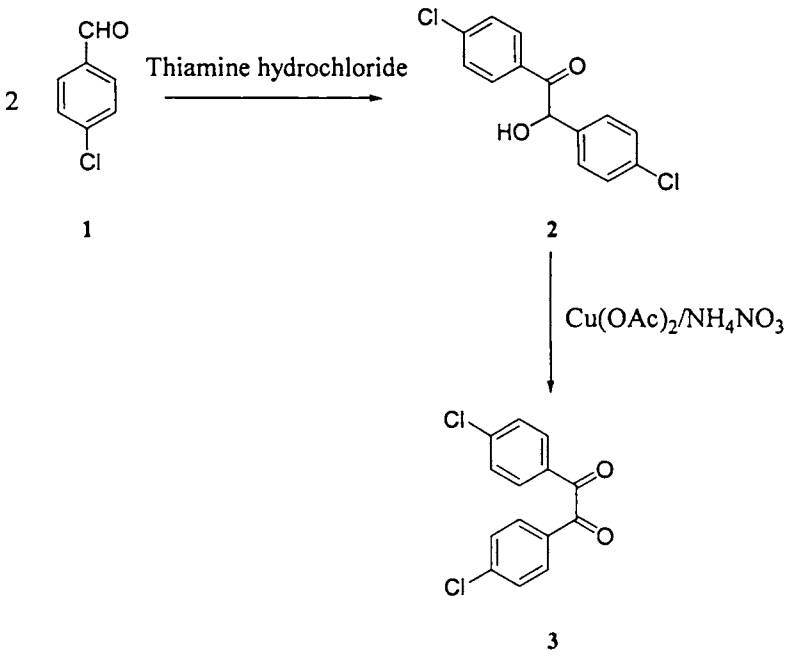
2.2. Results and Discussion

2.2.1. Synthesis of 1,2-Bis(4-chlorophenyl)-2-hydroxyethanone (2)

We adopted the well-known benzoin condensation reaction to prepare the title compound. Either potassium or sodium cyanide is used as a unique catalyst to effect benzoin condensation. Since cyanide ion is highly toxic, we adapted the bio-mimetic acyloin condensation pathway involving thiamine as a coenzyme[12,13] for preparing the required benzoin. Thiamine hydrochloride catalysed condensation of 4-chlorobenzaldehyde (**1**) provided **2** in high yields.

2.2.2. Synthesis of 4,4'-Dichlorobenzil (3)

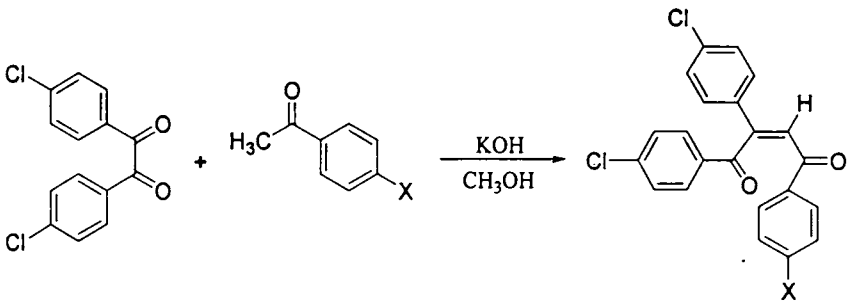
Concentrated nitric acid is commonly used for the oxidation of benzoins to the corresponding benzils. Though this is an efficient procedure, the toxic and corrosive nature of nitric acid and formation of nitrogen peroxide as a side product make this procedure less attractive to today's chemists. So, we adopted a more eco-friendly route to benzils. Thus, the oxidation of 1,2-bis(4-chlorophenyl)-2-hydroxyethanone (**2**) using catalytic amount of cupric acetate in the presence of stoichiometric amount of ammonium nitrate[14] produced 4,4'-dichlorobenzil, (**3**) in high yields (Scheme 1). The reaction proceeded under mild conditions and only minimal amount of undesirable side-products were formed in this case.



Scheme 1

2.2.3. Syntheses of 1-Aryl-3,4-bis(4-chlorophenyl)-but-2-ene-1,4-diones 5a-d

α,β-Unsaturated ketones are conveniently prepared by Claisen-Schmidt condensation.[15,16] which is the aldol condensation and subsequent elimination of a water molecule in presence of a basic catalyst. By the application of this reaction, we synthesized dibenzoylstyrene derivatives **5a-d** from 4,4'-dichlorobenzil (**3**) and appropriate methyl ketones (Scheme 2). In the present investigation, we employed acetophenone (**4a**), 4-chloroacetophenone (**4b**), 4-methylacetophenone (**4c**), and 4-methoxyacetophenone (**4d**). The products were obtained in good yields. The structure of adducts were established on the basis of analytical results and spectral data. On the basis of literature precedence,[17] *Z*-configuration was assigned to these molecules.



3 4a-d 5a-d

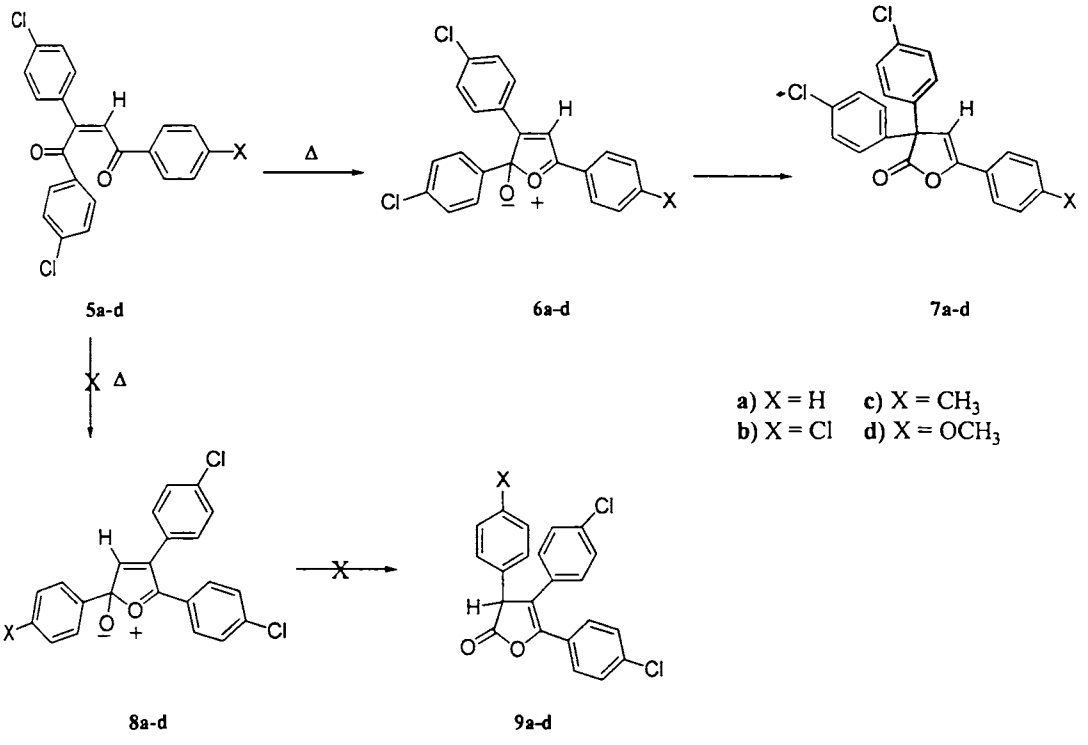
a) X = H c) X = CH_3
b) X =Cl d) X = OCH_3

Scheme 2

Compound *(Z)*-3,4-di(4-chlorophenyl)-1-phenyl-but-2-ene-1,4-dione **(5a)** was obtained in 40% yield and showed strong IR absorptions at 1662 and 1653 cm^{-1} due to two carbonyl groups present in this molecule. ^1H NMR spectrum showed a singlet at δ 7.2 corresponding to the vinylic proton and a multiplet at δ 7.2-7.8 corresponding to 13 aromatic protons in the molecule. Similarly *(Z)*-1,3,4-tri(4-chlorophenyl)-but-ene-1,4-dione **(5b)** obtained in 54% yield showed strong IR absorptions at 1666 and 1651 cm^{-1}. ^1H NMR spectrum showed a singlet at δ 7.2 due to vinylic proton and a multiplet at δ 7.3-8.0 corresponding to twelve aromatic protons. *(Z)*-3,4-Di(4-chlorophenyl)-1-(4-methylphenyl)-but-2-ene-1,4-dione **(5c)** obtained in 45% yield showed strong IR absorptions at 1668 and 1657 cm^{-1} due to two carbonyl groups in the compound. The compound showed a singlet at δ 2.4 corresponding to the three protons of the methyl group and a multiplet at δ 7.2-7.9 corresponding to one vinylic and twelve aromatic protons. *(Z)*-3,4-Di(4-chlorophenyl)-1-(4-methoxylphenyl)-but-2-ene-1,4-dione **(5d)** obtained in 46% yield showed strong IR absorptions at 1669 and 1654 cm^{-1} due to two carbonyls in the compound. The compound showed a singlet at δ 3.8 corresponding to the three protons of the methoxy group and a multiplet at δ 7.2-7.9 corresponding to one vinylic and twelve aromatic protons.

2.2.4. Synthesis of 5-Aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones 7a-d

Since 3,3,5-triphenyl-2(3H)-furanone is prepared in good yields by the thermolysis of dibenzoylstyrene[18,19] we reasoned that 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones **7a-d** may be conveniently prepared by the thermolysis of corresponding dibenzoylstyrene derivatives. Consequently, we synthesized a few 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones **7a-d** from the corresponding dibenzoylstyrene derivatives **5a-d** (Scheme 4). The structure of furanones **7a-d** was confirmed on the basis of spectral and analytical data.



Scheme 4

It is interesting to note that the isomeric furanone derivatives **9a-d** were not formed in any of the reactions studied by us. We ascribe this remarkable selectivity on the basis of electronic effects. The preferential formation of the furanone **7** in the thermal transformation may be rationalized in terms of the greater stability of the zwitterionic intermediate **6,** which is stabilized by the aryl

group present at the 3-position. This effect is lacking in the case of the competing zwitterionic intermediate **8** involved in the generation of **9**. Our conclusion is supported by literature precedences.[9-11,20]

3,3-Bis(4-chlorophenyl)-5-phenyl-3H-furan-2-one **(7a)** was obtained in 35% yield and showed strong IR absorptions at 1780 and 1653 cm^{-1} due to one carbonyl group and C=C group respectively in the compound. ^1H NMR spectrum showed a singlet at δ 5.9 corresponding to the vinylic proton and a multiplet at δ 7.1-7.6 corresponding to 13 aromatic protons in the molecule. Similarly 3,3,5-tris(4-chlorophenyl)-3H-furan-2-one **(7b)** obtained in 37% yield showed strong IR absorptions at 1784 and 1653 cm^{-1}. ^1H NMR spectrum of this compound showed a singlet at δ 6.1 corresponding to one vinylic proton and a multiplet at δ 7.2-7.6 corresponding to twelve aromatic protons. Similarly, 3,3-bis(4-chlorophenyl)-5-(4-methylphenyl)-3H-furan-2-one **(7c)** obtained in 44% yield showed strong IR absorptions at 1778 and 1653 cm^{-1} due to one carbonyl group and one C=C group respectively. The compound showed a singlet at δ 2.4 corresponding to the three protons of the methyl group, another singlet at δ 6.2 corresponding to one vinylic proton and a multiplet at δ 7.2-7.6 corresponding to twelve aromatic protons. 3,3-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-3H-furan-2-one **(7d)** obtained in 42% yield showed strong IR absorptions at 1778 and 1653 cm^{-1} due to one carbonyl group and one C=C group respectively. The compound showed a singlet at δ 3.8 corresponding to the three protons of the methoxy group, another singlet at δ 6.2 corresponding to one vinylic proton and a multiplet at δ 7.0-7.6 corresponding to twelve aromatic protons.

2.3. Conclusion

In summary, 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones were synthesized by the thermolysis of corresponding 1-aryl-3,4-di(4-chlorophenyl)-but-2-ene-1,4-dione precursors.

2.4. Experimental

2.4.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300, 400 and 500 MHz on a Bruker FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

2.4.2. Synthesis of 1,2-Bis(4-chlorophenyl)-2-hydroxyethanone (2)

Thiamine hydrochloride (2.462 g, 7.3 mmol) dissolved in 7 mL of water was cooled in an ice water bath. Methanol (21 mL) was added to it. Cold sodium hydroxide solution (4 M, 7 mL) was then added dropwise to the ice-cold mixture with shaking over a 10 minute period. Powered 4-chlorobenzaldehyde (**1**, 14.000 g, 100 mmol) was, added to this mixture and was refluxed gently on a steam bath for 90 minutes. It was then allowed to cool in an ice bath and scratched with a glass rod to induce crystallization. The precipitate was filtered and washed with cold water, dried and weighed. (22.480 g, 80%, mp 84 ^{0}C [21]).

2.4.3. Synthesis of 4,4'-Dichlorobenzil (3).

Cupric acetate (0.140 g, 0.7 mmol), ammonium nitrate (7.168 g, 89.6 mmol), 1,2-bis(4-chlorophenyl)-2-hydroxyethanone (20.007 g, 71.2 mmol) and 50 mL of 80% aqueous acetic acid were taken in a 250 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes.

Vigorous evolution of nitrogen was observed. The solid separated was collected by filtration and recrystallised from methanol to yield **3** (14.90 g, 75%; mp 197 ^{0}C [22]).

2.4.4. Synthesis of 1-Aryl-3,4-di(4-chlorophenyl)-but-2-ene-1,4-diones 5a-d

2.4.4.1. 3,4-Di(4-chlorophenyl)-1-phenyl-but-2-ene-1,4-dione (5a). A mixture of 4,4'-dichlorobenzil (**3**, 2.985 g, 10.7 mmol), acetophenone (**4a**, 1.524 g, 12.7 mmol) and powdered potassium hydroxide (0.400 g) in methanol (30 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **5a** as a light yellow solid.

Compound 5a: (1.631 g, 40%); mp 174 ^{0}C; IR (KBr) 1662 and 1653 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (s, 1H, vinylic), 7.3-8.1 (m, 14H, aromatic and vinylic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.3 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129 (CH), 129.1 (CH), 129.2 (CH), 129.5 (CH), 129.9 (CH), 130.2 (CH), 132.8 (CH), 133.6 (C), 134 (C), 134.2 (C), 136.9 (C), 139.9 (C), 154 (C), 189 (CO), 198 (CO); MS, *m/z* 381 (M^+), 383 (M^++2) and other peaks.

2.4.4.2. 1,3,4-Tris(4-chlorophenyl)-but-2-ene-1,4-dione (5b). A mixture of 4,4'-dichlorobenzil (**3**, 2.985 g, 10.7 mmol), 4-chloroacetophenone (**4b**, 1.963 g, 12.7 mmol) and powdered potassium hydroxide (0.400 g) in methanol (30 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **5b** as a light yellow solid.

Compound 5b: (2.397 g, 54%); mp 172 ^{0}C; IR (KBr) 1666 and 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (s, 1H, vinylic), 7.3-8.0 (m, 12H, aromatic); MS, *m/z* 415 (M^+), 417 (M^++2) and other peaks.

2.4.4.3. 3,4-Di(4-chlorophenyl)-1-(4-methylphenyl)-but-2-ene-1,4-dione (5c). A mixture of 4,4'-dichlorobenzil (**3**, 2.985 g, 10.7 mmol), 4-methylacetophenone (**4c**, 1.701 g, 12.7 mmol) and powdered potassium hydroxide

(0.400 g) in methanol (30 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **5c** as a light yellow solid.

Compound 5c: (1.902 g, 45%); mp 155 ^{0}C; IR (KBr) 1668 and 1657 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 7.2-7.9 (m, 13H, aromatic and vinylic).

2.4.4.4. 3,4-Di(4-chlorophenyl)-1-(4-methoxyphenyl)-but-2-ene-1,4-dione (5d). A mixture of 4,4'-Dichlorobenzil (**3**, 2.985 g, 10.7 mmol), methoxyacetophenone (**4d**, 1.905 g, 12.7 mmol) and powdered potassium hydroxide (0.400 g) in methanol (30 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **5d** as a light yellow solid.

Compound 5d: (2.023 g, 46%); mp 168 ^{0}C; IR (KBr) 1669 and 1654 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 7.2-7.9 (m, 13H, aromatic and vinylic).

2.4.5. Synthesis of 5-Aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones (7a-d)

2.4.5.1. 3,3-Bis(4-chlorophenyl)-5-phenyl-3H-furan-2-one (7a). A sample of **5a** (1.000 g, 2.6 mmol) was thermolysed in a sealed tube at 210 ^{0}C for 6 h. The residue was extracted with dichloromethane and chromatographed over silica gel. Elution with a mixture of (4:1) hexane and dichloromethane gave **7a** as a white solid.

Compound 7a: (0.347 g, 35%); mp 108 ^{0}C; IR (KBr) 1780 (C=O) and 1653 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (s, 1H, vinylic), 7.1-7.6 (m, 13H, aromatic); MS, *m/z* 381 (M^+) and other peaks; Anal. Calcd for $C_{22}H_{14}O_2Cl_2$: C, 69.31; H, 3.7. Found C, 69.2; H, 3.56.

Further elution of the column with dichloromethane gave unchanged **5a** (0.396 g, 40%).

2.4.5.2. 3,3,5-Tris(4-chlorophenyl)-3H-furan-2-one (7b). A sample of **5b** (1.000 g, 2.4 mmol) was thermolysed in a sealed tube at 210 ^{0}C for 6 h. The residue was extracted with dichloromethane and chromatographed over silica gel. Elution with a mixture of (4:1) hexane and dichloromethane gave **7b** as a white solid.

Compound 7b: (0.369 g, 37%); mp 116 ^{0}C; IR (KBr) 1784 (C=O) and 1653 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (s, 1H vinylic), 7.2-7.6 (m, 12H, aromatic); Anal. Calcd for $C_{22}H_{13}O_2Cl_3$: C, 63.56; H, 3.15. Found C, 63.50; H, 3.0.

Further elution of the column with dichloromethane gave unchanged **5b** (0.419 g, 42%).

2.4.5.3. 3,3-Bis(4-chlorophenyl)-5-(4-methylphenyl)-3H-furan-2-one (7c). A sample of **5c** (1.000 g, 2.5 mmol) was thermolysed in a sealed tube at 210 ^{0}C for 6 h. The residue was extracted with dichloromethane and chromatographed over silica gel. Elution with a mixture of (4:1) hexane and dichloromethane gave **7c** as a white solid.

Compound 7c: (0.434 g, 44%); mp 110 ^{0}C; IR (KBr) 1778 (C=O) and 1653 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), 6.2 (s, 1H vinylic), 7.2-7.6 (m, 12H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_3), 60.9 (C), 105.6 (C), 124.7 (CH), 125.0 (CH), 128.9 (CH), 129.1 (CH), 129.5 (C), 134.0 (C), 138.4 (C), 140.6 (C), 152.5 (C), 176.5 (CO); MS, *m/z* 395 (M^+), 397 (M^++2) and other peaks; Anal. Calcd for $C_{23}H_{16}O_2Cl_2$: C, 69.89; H, 4.08. Found C, 69.91, H, 3.9.

Further elution of the column with dichloromethane gave unchanged **5c** (0.395 g, 40%).

2.4.5.4. 3,3-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-3H-furan-2-one (7d). A sample of **5d** (1.000 g, 2.4 mmol) was thermolysed in a sealed tube at 210 ^{0}C for 6 h. The residue was extracted with dichloromethane and chromatographed over silica gel. Elution with a mixture of (4:1) hexane and dichloromethane gave **7d** as a white solid.

Compound 7d: (0.414 g, 42%); mp 112 ^{0}C; IR (KBr) 1778 (C=O) and 1653 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), 6.2 (s, 1H, vinylic), 7.0-7.6 (m, 12H, aromatic). Anal. Calcd for $C_{23}H_{16}O_3Cl_2$: C, 67.17; H, 3.92. Found C, 67.1; H, 3.98.

Further elution of the column with dichloromethane gave unchanged **5d** (0.374 g, 38%).

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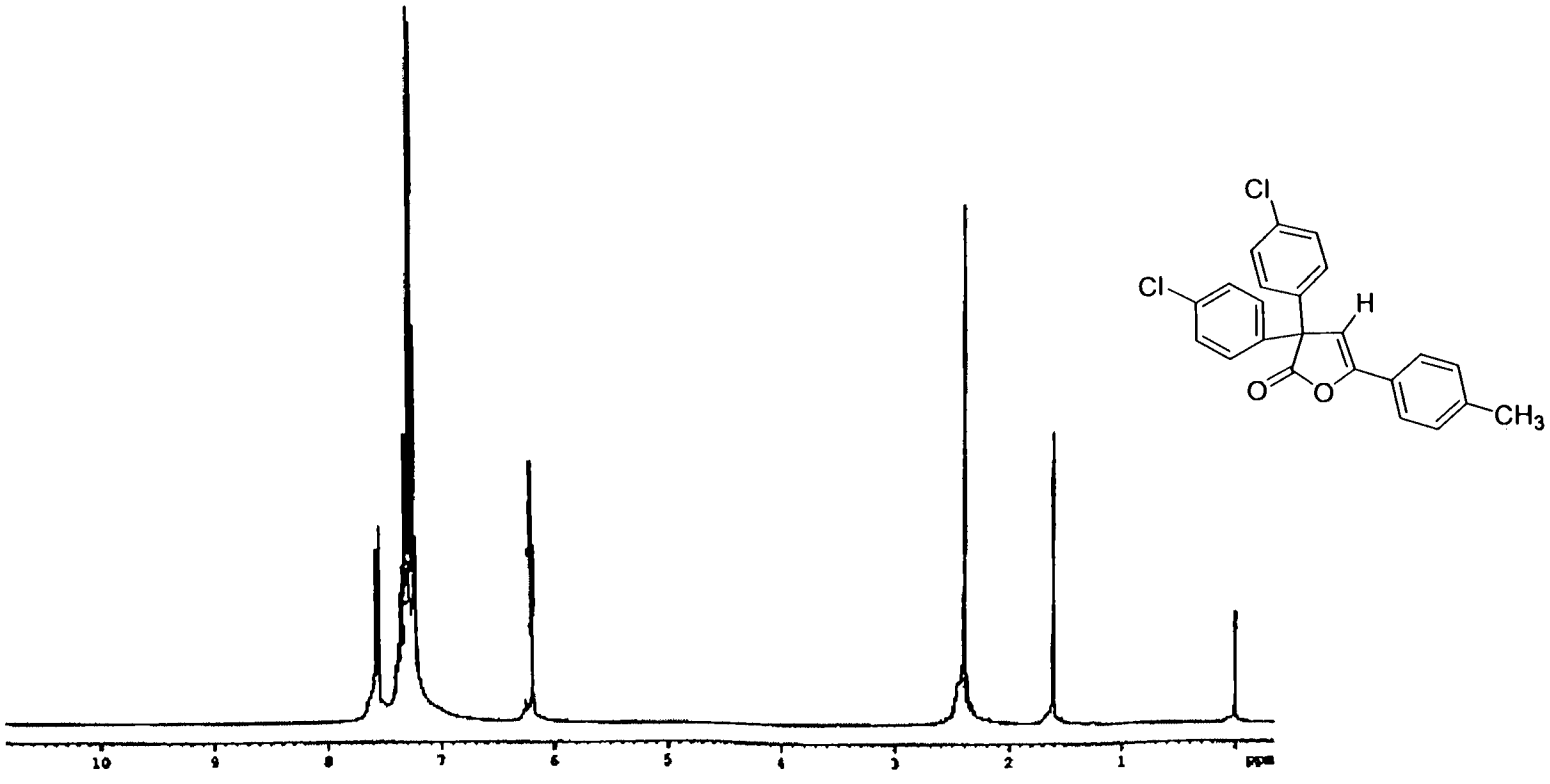


Figure 1. ^{1}H NMR Spectrum of Compound 7c

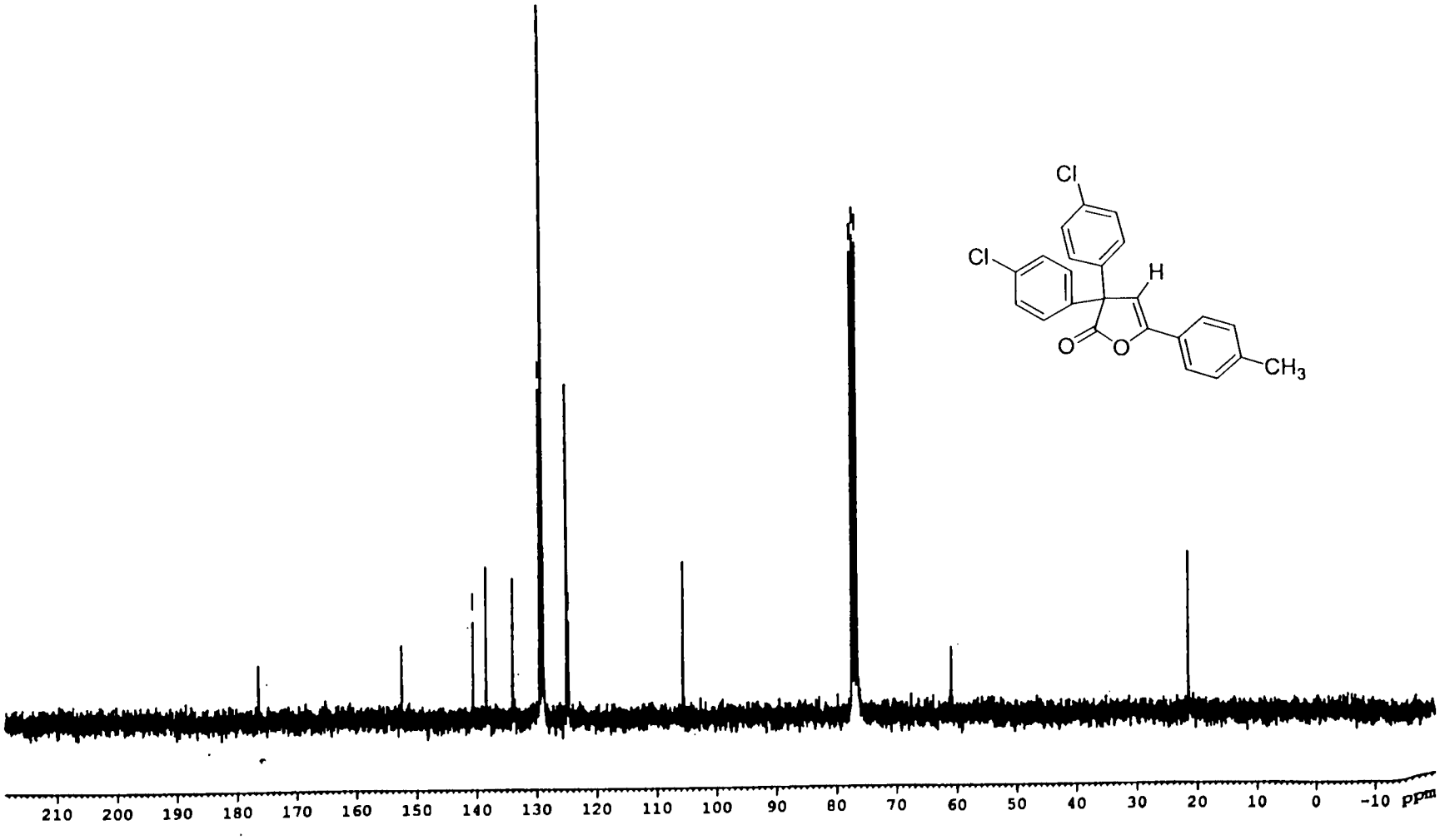


Figure 2. ^{13}C NMR Spectrum of Compound 7c

Chapter 3

ATTEMPTED SYNTHESIS OF A FEW 5-ARYL-3,3-DIPYRIDIN-2-YL-3H-FURAN-2-ONES

In an attempt to synthesise 5-aryl-3,3-dipyridie-2yl-3H-furan-2-ones, several 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-dione precursors were synthesised by the base-catalysed reaction between 2,2'-pyridil and suitably substituted acetophenones. These novel dibenzoylalkene-type systems containing heteroatomatic rings underwent extensive decomposition under the influence of both heat and light.

3.1. Introduction

3,3,5-Triaryl-2(3H)-furanones are known to undergo various interesting photochemical and thermal transformations.[1] The observed processes include decarbonylation,[2,3] decarboxylation,[4] solvent addition to double bonds,[5] aryl group migration,[6] and dimerisation.[7] The influence of the aryl groups on controlling the photochemical reactivity of 3,3.5-triaryl-2(3H)-furanones has been investigated in some detail. In the previous chapter, we have described the synthesis of several 5-aryl-3,3-bis(4-chlorophenyl)-3H-furan-2-ones. As a logical extension, we proposed to synthesise a few 2(3H)-furanones having heteroaromatic substituents. We reasoned that the presence of electron-withdrawing heteroaromatic substituents such as pyridine will have a substantial influence on the stability of the ionic intermediates[8-11] involved in the photochemical reaction pathways followed by these systems. Moreover, the presence of heteroaromatic substituents may potentially provide some hitherto unobserved photochemical pathways to these furanones. In order to examine the influence of heteroaromatic substituents on the photochemical pathways followed by 2(3H)-furanones, we proposed to synthesise a few 3,3.5-triaryl-2(3H)-furanones having heteroaromatic substituents. Based on the previous reports on the thermal transformations of dibenzoylstyrenes,[12-17] we identified 4-phenyl-1,2-

dipyridin-2-yl-but-2-ene-1,4-dione as a potential precursor to the required furanone derivative (Figure 1). In this chapter, we describe the synthesis of dibenzoylstyrene-type precursors and their transformations under the influence of heat and light.

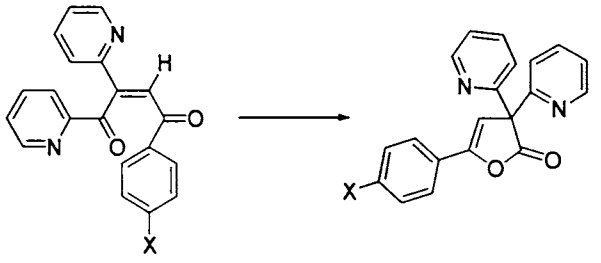


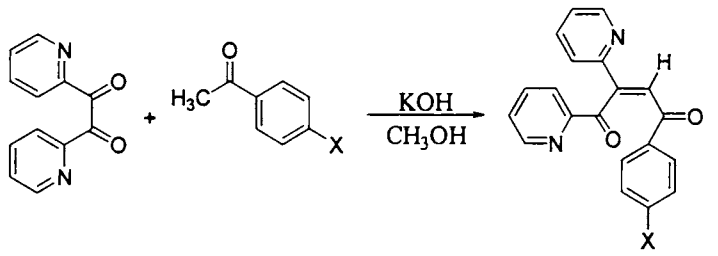
Figure 1

3.2. Results and Discussion

3.2.1. Syntheses of 4-Aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones 3 a-h.

A convenient method for the synthesis of dibenzoylalkenes involves the condensation of benzils with suitably substituted acetophenones. Japp and Klingemann in 1890 reported a simple and facile route for the synthesis of *(Z)*-dibenzoylstyrene by the condensation of benzil with acetophenone.[18] By the application of this reaction, we have successfully synthesized of a few *(Z)*-1-aryl-3,4-di(4-chlorophenyl)-but-2-ene-1,4-diones from 4,4'-dichlorobenzil and suitably substituted acetophenones. Based on these observations we reasoned that the reaction of 2,2'-pyridil with acetophenone should provide a simple route for the synthesis of the corresponding *(Z)*-dibenzoylalkene-type system containing pyridine substituents. Accordingly we carried out the base-catalysed condensation of 2,2'-pyridil with suitably substituted acetophenones. For the present investigation, we chose acetophenone **(2a)**, 4-methylacetophenone **(2b)**, 4-methoxyacetophenone **(2c)**, 4-ethoxyacetophenone **(2d)**, 4-fluoroacetophenone (2e), 4-chloroacetophenone **(2f)**, 4-bromoacetophenone **(2g)**, and 4-cyclohexylacetophenone **(2h)** (Scheme 1). 4-Aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones **3a-h** were obtained in good yields. The reaction between 2,2'-pyridil and acetophenone was found to be faster than the corresponding reaction between

benzil and acetophenone. However, 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones were found to be unstable in solution. The solution turned dark on brief exposure to light. Consequently, all operations involving this material were done under strict exclusion of light. The structure of adducts were established on the basis of analytical results and spectral data. Tentative prediction of stereochemistry of these systems was done on the basis of literature precedence and available spectral data (*vide infra*).



1 2 a-h 3 a-h

a) X = H
b) X = CH_3
c) X = OCH_3
d) X = OEt
e) X = F
f) X = Cl
g) X = Br
h) X = C_6H_{11}

Scheme 1

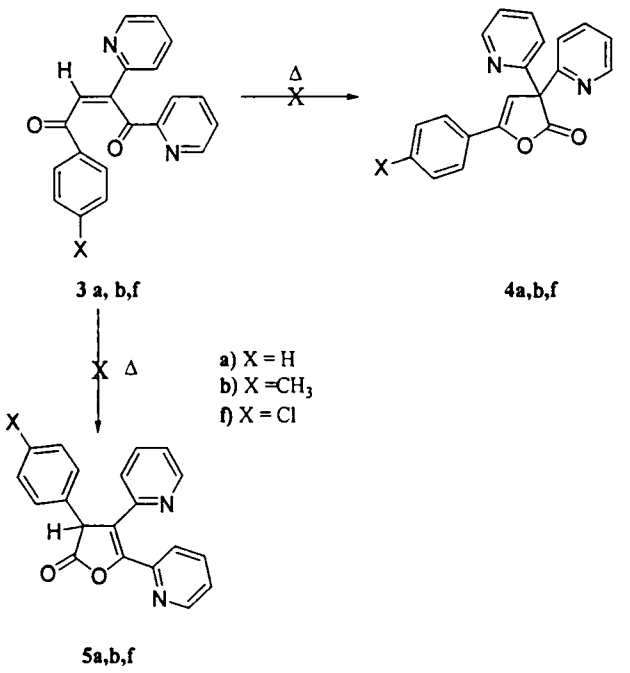
4-Phenyl-1,2-dipyridin-2-yl-but-2-ene-1,4-dione (**3a**) was obtained in 50% yield and showed strong IR absorptions at 1694 and1650 cm^{-1} due to two carbonyl groups present in the compound. Close examination of the ^1H NMR spectrum of this compound indicated the presence of a singlet at δ 8.3 (s, 1H) ascribable to the vinylic proton. Based on the position of the signal due the vinylic proton, we assigned *Z*-configuration to the newly-synthesised dibenzoylstyrene-type systems *(vide infra).* Similarly, 1,2-dipyridin-2-yl-4-*p*-tolyl-but-2-ene-1,4-dione (**3b**) obtained in 43% yield showed strong IR absorptions at 1693 and 1653 cm^{-1} due to two carbonyl groups in the compound. The compound showed a singlet at δ 2.4 corresponding to the three protons of the methyl group, a singlet at δ 8.3 due to vinylic proton and a multiplet at δ 7.2-8.9 corresponding to twelve aromatic protons. 4-(4-Methoxyphenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione (**3c**) obtained in 45% yield showed strong IR absorptions at 1686and 1643 cm^{-1} due to two carbonyls in the compound. The

compound showed a singlet at δ 3.8 corresponding to the three protons of the methoxy group, a singlet at δ 8.3 due to one vinylic proton and a multiplet at δ 7.2-8.9 corresponding to twelve aromatic protons. 4-(4-Ethoxyphenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione **(3d)** obtained in 42% yield shows strong IR absorptions at 1688 and 1648 cm^{-1} due to two carbonyls in the compound. The compound showed a triplet at δ 1.3 corresponds to methyl protons, a quartet at δ 3.9 corresponding to the two protons of the methylene group, a singlet at δ 8.3 due to one vinylic proton and a multiplet at δ 7.0-8.9 corresponding to twelve aromatic protons. 4-(4-Fluorophenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione **(3e)** obtained in 35% yield showed strong IR absorptions at 1692 and 1653 cm^{-1} due to two carbonyls in the compound. The compound showed a singlet at δ 8.3 due to one vinylic proton and a multiplet at δ 7.2-8.8 corresponding to twelve aromatic protons. 4-(4-Chlorophenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione **(3f)** obtained in 45% yield showed strong IR absorptions at 1693 and 1655 cm^{-1}. ^1H NMR spectrum showed a singlet at δ 8.3 due to one vinylic proton and multiplet at δ 7.5-8.9 corresponding to twelve aromatic protons. 4-(4-Bromophenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione **(3g)** obtained in 35% yield showed strong IR absorptions at 1693 and 1654 cm^{-1} due to two carbonyls in the compound. The compound showed a singlet at δ 8.3 due to one vinylic proton and a multiplet at δ 7.2-8.7 corresponding to twelve aromatic protons. 4-(4-Cyclohexylphenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione **(3h)** obtained in 36% yield shows strong IR absorptions at 1697 and 1653 cm^{-1} due to two carbonyls in the compound. The compound showed a multiplet centered at δ 1.3 due to six methylene protons, another multiplet centered at δ 1.6 corresponding to four methylene protons, multiplet at δ 2.6 corresponding to the methane proton, a singlet δ 8.3 corresponding to one vinylic proton and peak δ 7.2-8.9 corresponding to twelve aromatic protons.

3.2.2. Attempted Synthesis of 5-Aryl-3,3-dipyridin-2-yl-3H-furan-2-ones

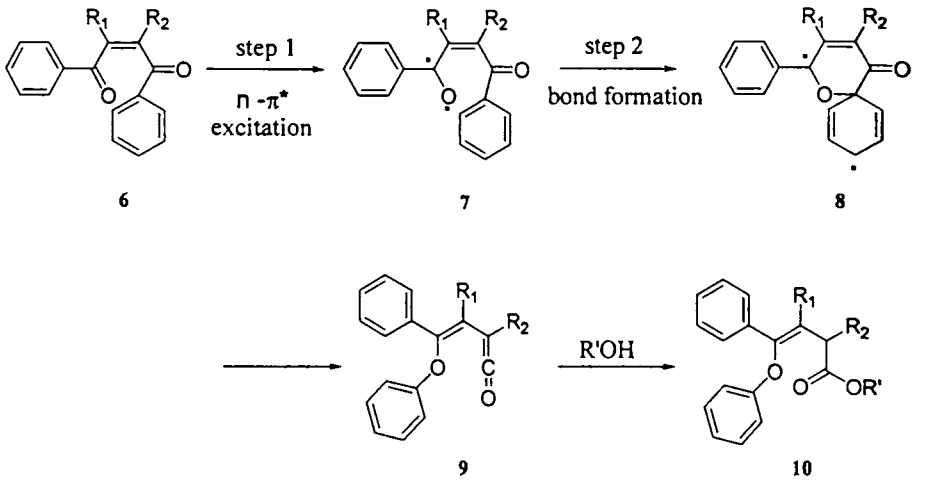
A convenient method for the synthesis of 2(3H)-furanones is by the thermolysis of corresponding dibenzoylalkene precursors.[16,17,19] Close

examination of the structural features of 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones indicates their similarity with dibenzoylstyrene. So we expected these dibenzoylstyrene-type systems to give corresponding 2(3H)-furanones on thermolysis. It may be mentioned here that the thermolysis of dibenzoylstyrenes may lead to the formation of two isomeric lactones. Based on electronic factors, path A is expected to be the major pathway followed by simple dibenzoylstyrenes. So, it was of interest to us to explore the effect of the pyridine substituent at the 2-position on the regiochemistry of the furanisation reaction. Unfortunately we could not synthesise the corresponding 2(3H)-furanones **4** or **5** by the thermolysis of **3**. Both neat as well as solvent-mediated thermolysis of representative examples such as **3a,b,f** resulted in complete charring of the reactant (Scheme 2).



Scheme 2

The photochemistry of dibenzoylalkenes is equally interesting.[20-34] Earlier reports indicate that upon irradiation, dibenzoylalkenes undergo cis-trans isomerisation and 1,5-aryl migration to oxygen leading to ketene intermediates (also known as dibenzoylalkene or Zimmermann rearrangement[23]) (Scheme 3).

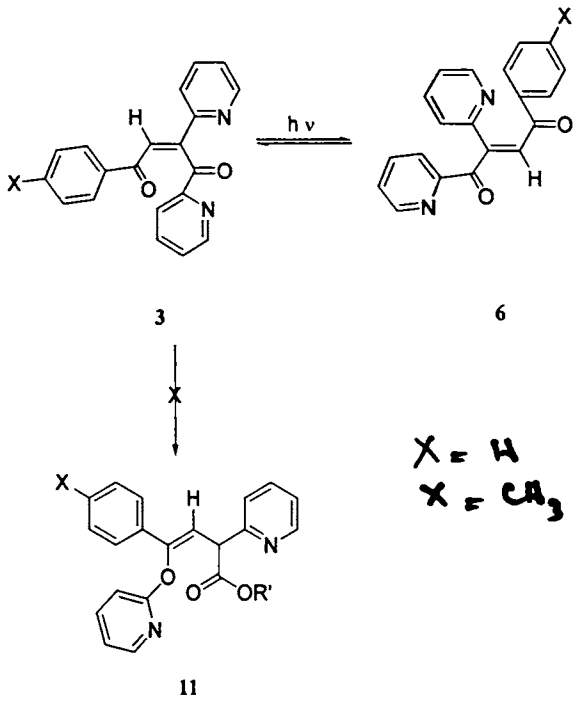


Scheme 3

As a part of our continued interest in the photochemistry of dibenzoylalkenes, we have explored the possibility of synthesising several dibenzoylalkene type systems.[35,36] So, it was of special interest to us to examine the photochemistry of 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones incorporating pyridine substituents synthesised by us. If these novel dibenzoylalkene-type systems are to behave like typical dibenzoylalkenes, upon irradiation, they should undergo both cis-trans isomerisation and aryl group migration to oxygen leading to ketene-derived products (Scheme 4). Thus, with a view to establish the generality of dibenzoylalkene rearrangement, we examined the photochemistry of **3**. In order to obtain preliminary data on the nature of the products obtained in the irradiation of these dibenzoylalkene-type systems, we recorded the ^{1}H NMR spectrum of the photolysate obtained from a typical example such as **3b**. For this experiment, we used dichloromethane as the solvent. The ^{1}H NMR spectra of the **3b** and the crude product mixture obtained in the irradiation **3b** at 350 nm are given in Figure 4. Total consumption of **3b** is indicated by the disappearance of the vinyl signal at δ 8.3 and also by the shift in the signal due to the methyl substituent at δ 2.4 to δ 2.3 region. It is interesting to notice that a new singlet is observed at δ 9.0. We attributed this signal to the vinyl protons of the trans-isomer **6b**. The appearance of two signals of nearly equal intensity around δ 2.3 indicates the formation of two new products in nearly equal amounts. However, the absence of the signal expected at δ 5.3 due to the

methine protons of **11** precludes the possibility of dibenzoylalkene rearrangement. Based on these results, we infer that irradiation of **3** does not lead to dibenzoylalkene rearrangement. However, cis-trans isomerisation is a distinct possibility here. Furthermore, we employed the results obtained from this experiment to support our designation of the stereochemistry of **3** as cis since with typical dibenzoylaklens, it has generally been observed that the vinyl protons in the trans isomer appears downfield shifted with respect to that of the cis isomer.[37]

However, the results obtained from preparative photochemistry of **3** presented a very different picture. Irradiation of **3** in solvents such as benzene and methanol gave dark-coloured solutions. TLC analysis the photolysate obtained here also indicated substantial consumption of **3** and the generation of new products. Based on the results obtained from the NMR analysis discussed above, we concluded that **6** is formed as a major photoproduct. However, our attempts to isolate the new photoproducts including **6** were unsuccessful. Instead, we recovered unchanged **3** in substantial amounts. We attribute this seemingly anomalous result to the facile isomerisation of the trans-isomer obtained as photoproduct to the corresponding cis isomer. Our assumption is based on an earlier report by Zimmermann[23] indicating that dibenzoylakenes undergo cis-rtrans isomerization under conditions of workup.



Scheme 4

3.3. Conclusion

In order to generalise the photochemical pathways followed by 2(3H)-furanones, we attempted the synthesis of a few novel 2(3H)-furanones containing pyridine ring residues: 5-aryl-3,3-dipyridin-2-yl-3H-furan-2-ones from the corresponding dibenzoylstyrene-type systems. We successfully synthesized several 4-aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones such as **3a-h** by the base catalysed condensation of 2,2'-pyridil **(1)** with various acetophenones **2**. These dibenzoylalkene-type systems underwent complete decomposition on thermolysis. On photolysis, they underwent cis-trans isomerisation similar to other dibenzoylalkenes.

3.4. Experimental

3.4.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried

and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow. All steady state irradiations were carried out using Rayonet Photochemical Reactor. Solvents for photolysis were purified and distilled before use.

3.4.2. Synthesis of 4-Aryl-1,2-dipyridin-2-yl-but-2-ene-1,4-diones 3a-h

3.4.2.1. 4-Phenyl-1,2-dipyridin-2-yl-but-2-ene-1,4-dione (3a). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), acetophenone (1.938 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3a** as a light yellow solid.

Compound 3a: (2.222 g, 50%); mp 144 ^{0}C; IR (KBr) 1694 and1650 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (s, 1H, vinylic), δ 7.4-8.7 (m, 13H, aromatic); MS, *m/z* 314 (M^{+}) and other peaks. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42, H, 4.49, N, 8.91. Found: C, 76.33, H, 4.54, N, 8.71.

3.4.2.2. 1,2-Dipyridin-2-yl-4-*p*-tolyl-but-2-ene-1,4-dione (3b). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-methylacetophenone (2.164 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3b** as a light yellow solid.

Compound 3b: (1.996 g, 43%); mp 155 ^{0}C; IR (KBr) 1693 and 1653 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 8.3 (s, 1H, vinylic), 7.2-8.9 (m, 12H, aromatic). Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81, H, 4.91, N, 8.53. Found: C, 76.68, H, 4.55, N, 8.49.

3.4.2.3. 4-(4-Methoxyphenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione (3c). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-methoxyacetophenone (2.423 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3c** as a light yellow solid.

Compound 3c: (2.190 g, 45%); mp 154 ^{0}C; IR (KBr) 1686 and 1643 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 8.3 (s, 1H, vinylic), δ 7.2-8.7 (m, 12H, aromatic); ^{13}C NMR (~~300 MHz~~, $CDCl_3$) δ 55.2 (OCH_3), 113.6 (CH), 121.8 (CH), 122.5 (CH), 123.3 (CH), 123.9 (CH), 126.5 (CH), 130.1 (CH), 130.9 (CH), 136.4 (CH), 136.7 (CH), 148.9 (CH), 149.7 (C), 152.9 (C), 153.7 (C), 154.4 (C), 163.6 (C), 187.2 (CO), 198.2 (CO); ^{13}C DEPT (~~300 MHz~~, $CDCl_3$, CH only) δ 149.7, 148.9, 136.7, 136.4, 130.9, 126.5, 123.9, 123.2, 122.5, 121.8, 113.6, 55.2; MS, *m/z* 344 (M^+) and other peaks. Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24, H, 4.68, N, 8.13. Found: C, 73.08, H, 4.06, N, 8.12.

3.4.2.4. 4-(4-Ethoxyphenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione (3d). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-ethoxyacetophenone (2.649 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3d** as a light yellow solid.

Compound 3d: (2.127 g, 42%); mp 158 ^{0}C; IR (KBr) 1688 and 1648 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (triplet, 3H, CH_3), δ 3.9 (quartet, 2H, CH_2), δ 8.3 (s, 1H, vinylic), δ 7.0-8.9 (m, 12H, aromatic); MS, *m/z* 358 (M^+) and other peaks. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73, H, 5.06, N, 7.82. Found: C, 73.70, H, 5.04, N, 7.79.

3.4.2.5. 4-(4-Fluorophenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione (3e). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-fluoroacetophenone (2.229 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3e** as a light yellow solid.

Compound 3e: (1.644 g, 35%); mp 160 ^{0}C; IR (KBr) 1692 and 1653 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (s, 1H, vinylic), δ 7.2-8.8 (m, 12H, aromatic); MS, *m/z* 332 (M^+) and other peaks. Anal. Calcd for $C_{20}H_{13}FN_2O_2$: C, 72.28, H, 3.94, N, 8.43. Found: C, 72.09, H, 3.73, N, 8.47.

3.4.2.6. 4-(4-Chlorophenyl)-1,2-dipyridin-2-yl-but-2-ene-1,4-dione (3f). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-chloroacetophenone (2.487 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3f** as a light yellow solid.

Compound 3f: (2.216 g, 45%); mp 172 ^{0}C; IR (KBr) 1693 and 1655 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (s, 1H, vinylic), δ 7.5-8.9 (m, 12H, aromatic); MS, *m/z* 348 (M^+) and other peaks. Anal. Calcd for $C_{20}H_{13}ClN_2O_2$: C, 68.87, H, 3.76, N, 8.03. Found: C, 68.76, H, 3.70, N, 7.94.

3.4.2.7. 4-(4-Bromophenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione (3g). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-bromoacetophenone

(3.214 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3g** as a light yellow solid.

Compound 3g: (1.946 g, 35%); mp 168 ^{0}C; IR (KBr) 1693 and 1654 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (s, 1H, vinylic), δ 7.2-8.7 (m, 12H, aromatic); MS (FAB), *m/z* 393 (M^+), 395 $(M+2)^+$ and other peaks. Anal. Calcd for $C_{20}H_{13}BrN_2O_2$: C, 61.09, H, 3.33, N, 7.12. Found: C, 61.06, H, 3.28, N, 7.09.

3.4.2.8. 4-(4-Cyclohexylphenyl)-1,2-di-pyridin-2-yl-but-2-ene-1,4-dione (3h). A mixture of 2,2'-pyridil (3.000 g, 14.15 mmol), 4-cyclohexylacetophenone (3.262 g, 16.15 mmol) and powdered potassium hydroxide (0.570 g) in methanol (17 mL) was stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3h** as a light yellow solid.

Compound 3h: (2.017 g, 36%); mp 172 ^{0}C; IR (KBr) 1697 and 1653 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (m, 6H, CH_2), 1.6 (m, 4H, CH_2), 2.6 (m, 1H, CH), δ 8.3 (s, 1H, vinylic), 7.2-8.9 (m, 12H, aromatic); ^{13}C NMR (~~300~~ 75 MHz, $CDCl_3$) δ 25.9 (CH_2), 26.6 (CH_2), 33.9 (CH_2), 44.6 (CH), 122.0 (CH), 122.7 (CH), 123.5 (CH), 124.2 (CH), 126.7 (CH), 127.0 (CH), 128.9 (CH), 135.1 (CH), 136.6 (CH), 136.8 (CH), 149.1 (CH), 149.9 (C), 153.1 (C), 153.8 (C), 154.0 (C), 154.8 (C), 188.5 (CO), 198.3 (CO); ^{13}C DEPT (~~300~~ 75 MHz, $CDCl_3$, CH only) δ 149.9, 149.1, 136.8, 136.6, 128.9, 127.0, 126.7, 124.2, 123.5, 122.7, 122.0, 44.6; MS, *m/z* 396 (M^+) and other peaks. Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76, H, 6.10, N, 7.07. Found: C, 78.72, H, 5.45, N, 7.03.

3.4.3. Attempted Thermolysis of 3a

3.4.3.1. Neat Thermolysis. A sample of **3a** (1.500 g, 4.8 mmol) was heated in a sealed tube around 180 ^{0}C for 2 h. The solid was extracted with dichloromethane. TLC showed complete decomposition of the starting material.

3.4.3.2. Thermolysis in Xylene. A sample of **3a** (1.000 g, 3.2 mmol) was refluxed in 80 mL xylene for 1 h. Solvent was removed and analysis of the residue was by TLC showed complete decomposition of the starting material.

Similar results were obtained when **3b** and **3f** were subjected to thermolysis by neat heating as well as heating in refluxing xylene.

3.4.4. Phtochemical Transformation of 3a

3.4.4.1. Irradiation of 3a in Benzene. A benzene solution of **3a** (0.079 g, 0.25 mmol in 250 mL) purged with nitrogen for 20 min was irradiated (RPR, 350 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was charged to a column of silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3a.** (0.047 g, 60%).

3.4.4.2. Irradiation of 3a in Methanol. A methanol solution of **3a** (0.079 g, 0.25 mmol in 250 mL) purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was charged to a column of silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3a** (0.049 g, 62%).

3.4.4.3. Irradiation of 3a in Dichloromethane. A dichloromethane solution of **3a** (0.079 g, 0.25 mmol in 250 mL) purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was charged to a column of silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3a** (0.051 g, 64%).

3.4.5. Photochemical Transformation of 3b

3.4.5.1. Irradiation of 3b in Benzene. A solution of **3b** (0.082 g, 0.21 mmol in 200 mL) in benzene purged with nitrogen for 20 min was photolysed under an RPR (350 nm, quartz vessel) light source for 6 h. The progress of the reaction was monitored by TLC. Removal of the solvent under vacuum gave a residue, which was chromatographed over silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3b** (0.05 g, 64%).

3.4.5.2. Irradiation of 3b in Methanol. A solution of **3b** (0.066 g, 0.20 mmol in 200 mL) in methanol purged with nitrogen for 20 min was photolysed under an RPR (350 nm, quartz vessel) light source for 2 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was charged to a column of silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3b** (0.04 g, 62%).

3.4.5.3. Irradiation of 3b in Dichloromethane. A solution of **3b** (0.066 g, 0.20 mmol in 200 mL) in dichloromethane purged with nitrogen was photolysed under an RPR (350 nm, quartz vessel) light source for 2 h. The progress of the reaction was monitored by TLC. A small portion of the photolysate, after removal of solvent under reduced pressure, was subjected to NMR analysis. Removal of the solvent under vacuum gave a residue, which was chromatographed over silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave unchanged **3b** (0.04 g, 63%).

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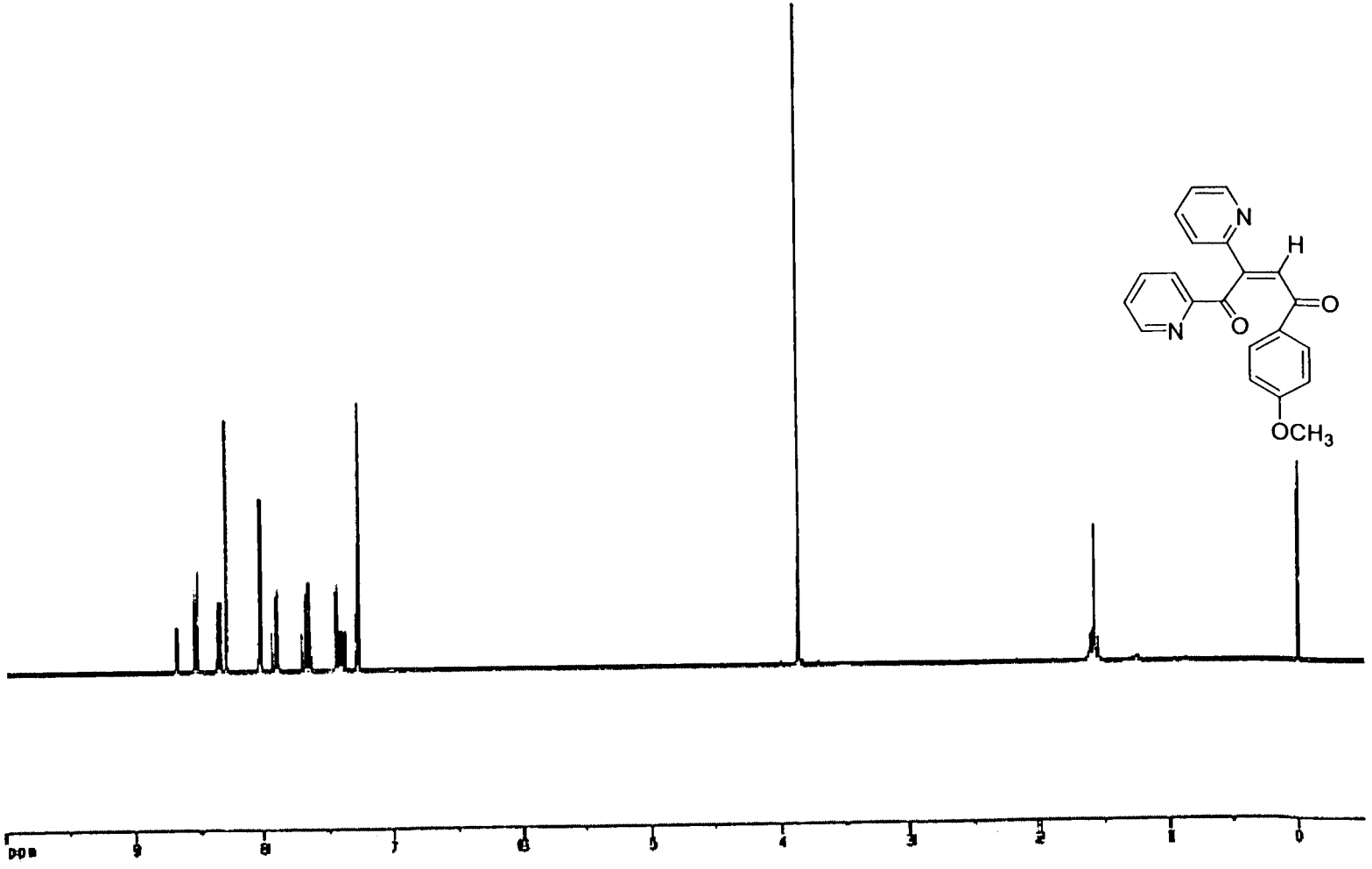


Figure 2. ^{1}H NMR Spectrum of compound 3c

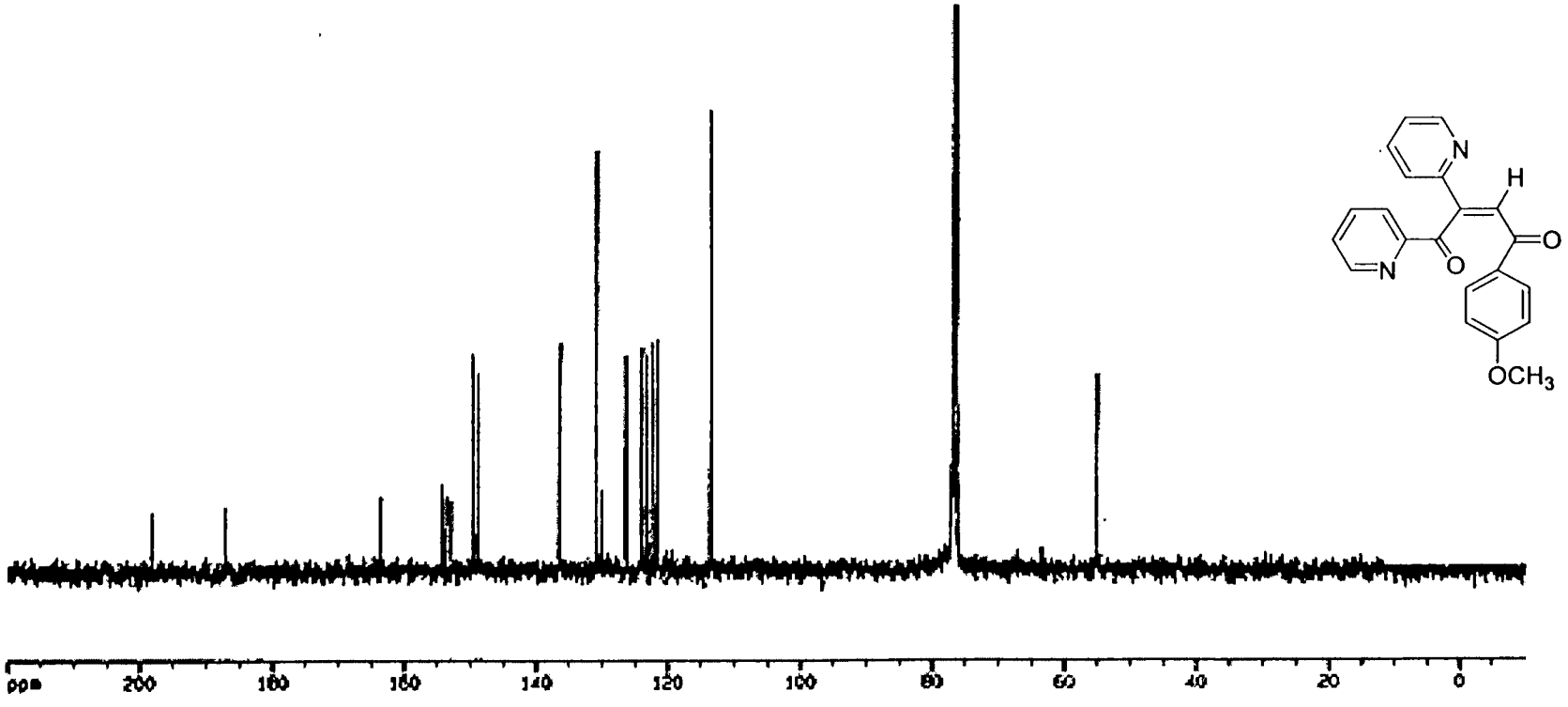


Figure 3. ^{13}C NMR Spectrum of Compound 3c

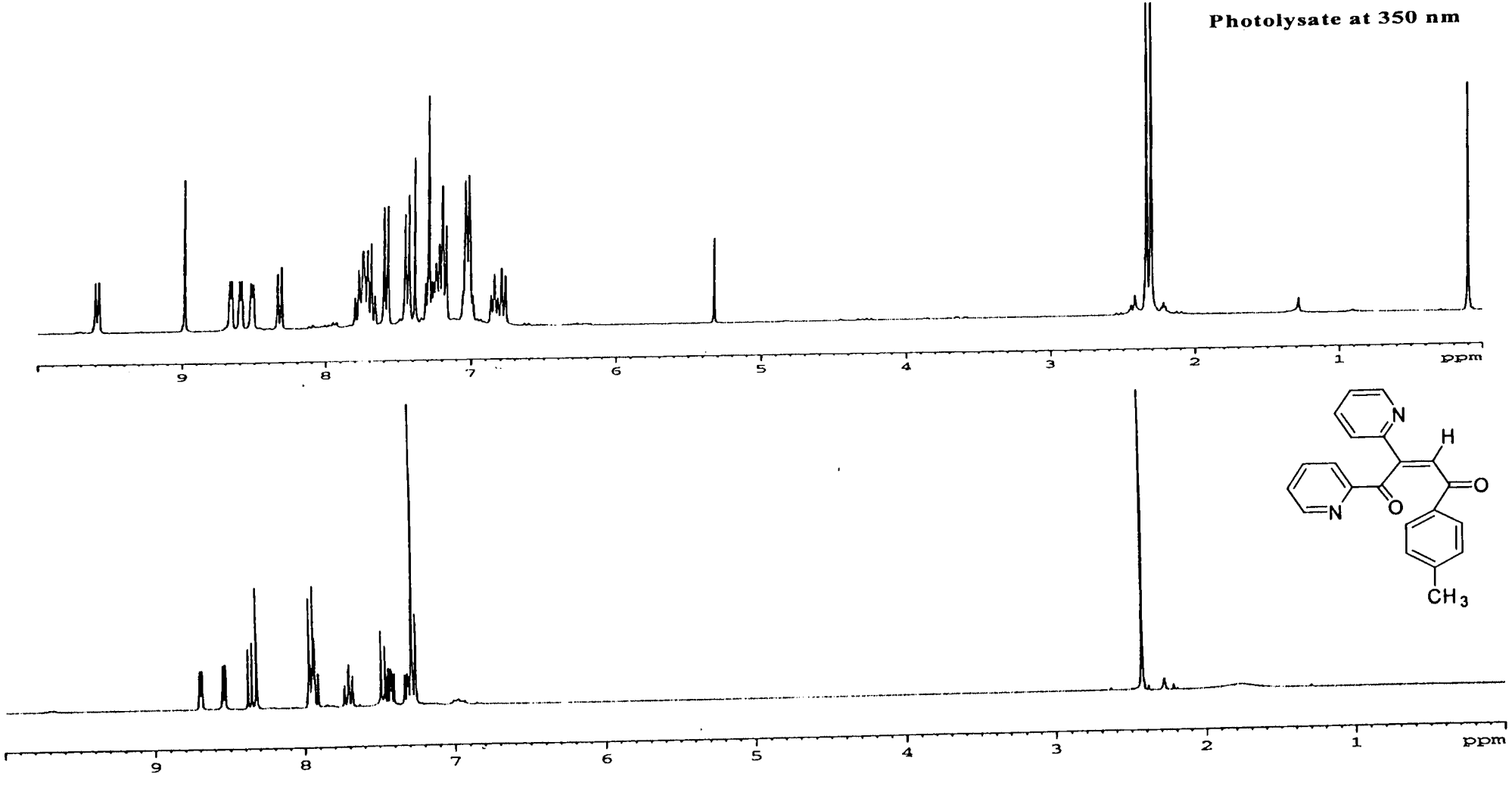


Figure 4. ^{1}H NMR Spectrum of Compound 3b and photolysate of 3b at 350 nm

Chapter-4

SYNTHESIS OF 2-ACETOXY-2-ARYL-4,5-DIPHENYL-2H-FURAN-3-ONES

3(2H)-Furanone ring system constitutes the central structural unit in many antitumor agents. We have developed an efficient method for the synthesis of several 3(2H)-furanones. The protocol developed by us employs readily available dibenzoylalkenes as starting materials and provides easy access to differently functionalized 3(2H)-furanones in four steps. The synthesis of a few 2-acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones is discussed in this chapter.

4.1. Introduction

The synthesis and reactions of 2(3H)-, 2(5H)-, and 3(2H)-furanones have attracted considerable attention.[1-38] While most of the investigations on 2(3H)- and 2(5H)-furanones were directed at unraveling the mechanistic underpinnings of their remarkable photochemistry, 3(2H)-furanones were investigated for their potential antitumor activity.[39-41] Only very few reports are available on the photochemistry of 3(2H)-furanones and available reports indicate that 3(2H)-furanones undergo fragmentation reaction under the influence of light. Upon irradiation, simple 2(3H)- and 2(5H)-furanones also undergo fragmentation and hydrogen abstraction reactions. In contrast 3,3,5-triaryl-2(3H)-furanones, and 3,5,5-triaryl-2(3H)-furanones undergo a variety of light-induced transformation including aryl group migration. 3,4,5-Triaryl-2(5H)-furanones and 3,3,4,5-tetraarylfuranones undergo electrocyclic reactions leading to the corresponding phenanthrofuranones. Acyl substituted furanones undergo radical fragmentation to give acyl and furanone radicals and consequent radical coupling reactions.[42] So, it was of interest to us to investigate the hitherto unknown photochemistry of triaryl-3(2H)-furanone.

Though efficient methods are available for the targeted synthesis of 2(3H)- and 2(5H)-furanones having desired substitution patterns, such general procedures are not available for the synthesis of triaryl-3(2H)-furanones. One of the few methods available for the synthesis of triarly-3(2H)-furanone employs dibenzoylalkenes as starting materials. It may be recalled in this connection that dibenzoylalkenes are commonly used precursors for 2(3H)-furanones as well. As a logical extension of our continued interest in the synthesis and chemistry of dibenzoylalkenes and dibenzoylalkene-type systems,[43] we targeted the synthesis of 3(2)-furanones from dibenzoylalkene precursors.

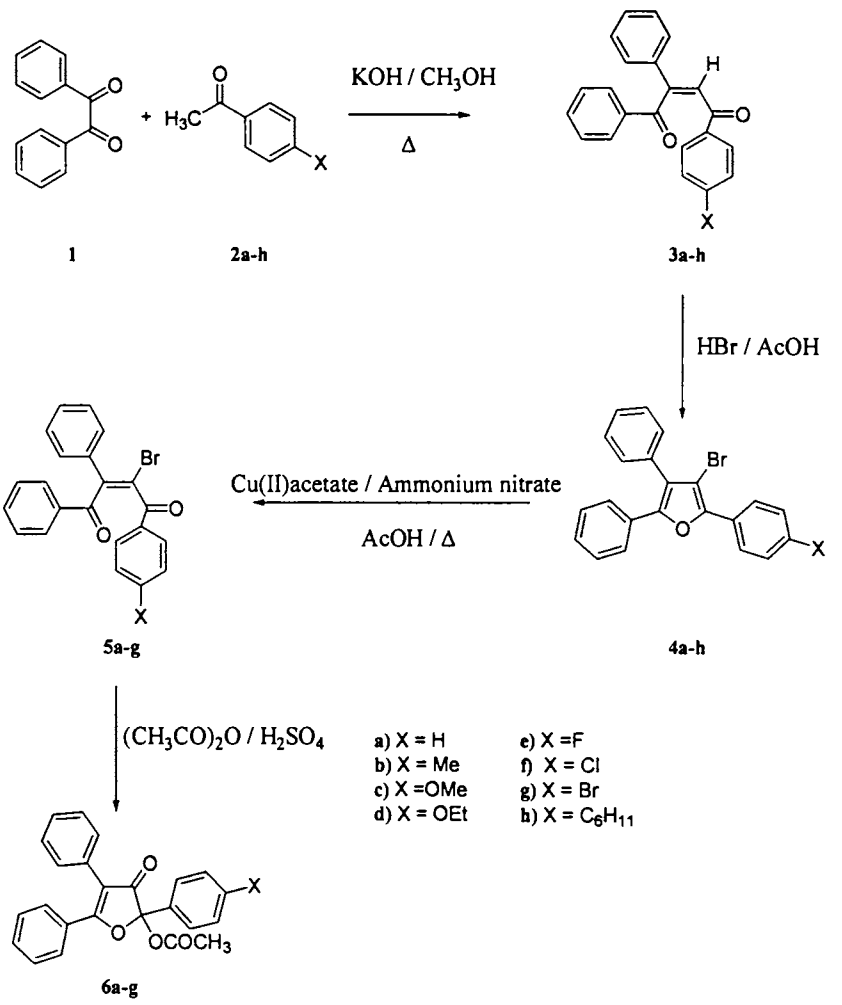
When we undertook the synthesis of 3(2H)-furanones, we addressed the following general questions:

1) Can we develop an efficient and general method for the synthesis of 2,4,5-triaryl-3(2H)-furanones starting from suitable dibenzoylalkenes?

2) Can we introduce different functional groups (some of which will undergo radical cleavage in the excited state) at the 2-position of 3(2H)-furanone ring system?

3) Will the 3(2H)-furanones synthesized by us exhibit antitumor properties?

In this context, we explored the possibility of developing a new and general approach to the synthesis of 3(2H)-furanones from simple and readily available starting materials such as 4-aryl-1,2-diphenylbut-2-ene-1,4-diones(dibenzoylstyrenes). The four-step process developed by us is summarized in Scheme 1.



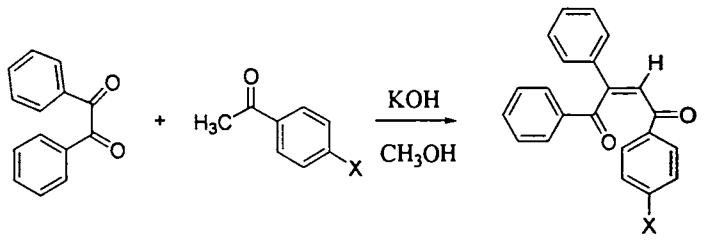
Scheme-1

4.2. Results and Discussion

4.2.1. Synthesis of 4-Aryl-1,2-diphenyl-but-2-ene-1,4-diones (3a-h)

α,β-Unsaturated ketones are conveniently prepared by Claisen-Schmidt condensation.[42,44] It is the aldol condensation and subsequent elimination of a water molecule in presence of base. By the application of this reaction, we synthesised dibenzoylstyrene derivatives, 4-aryl-1,2-diphenyl-but-2-ene-1,4-diones **3a-h**, from benzil **(1)** and appropriate methyl ketones (Scheme 2). In the present investigation, we employed acetophenone **(2a)**, 4-methylacetophenone **(2b)**, 4-methoxyacetophenone **(2c)**, 4-ethoxyacetophenone **(2d)**, 4-fluroacetophenone **(2e)**, 4-chloroacetophenone **(2f)**, 4-bromoacetophenone **(2g)**, 4-cyclohexylacetophenone **(2h)**. The products were obtained in good yields. The structure of the adducts

were established on the basis of analytical results and spectral data. On the basis of literature precedence,[45] *Z*-configuration was assigned to these molecules.



1 2a-h 3a-h

a) X = H
b) X = Me
c) X =OMe
d) X = OEt
e) X =F
f) X = Cl
g) X = Br
h) X = C_6H_{11}

65-70%

Scheme 2

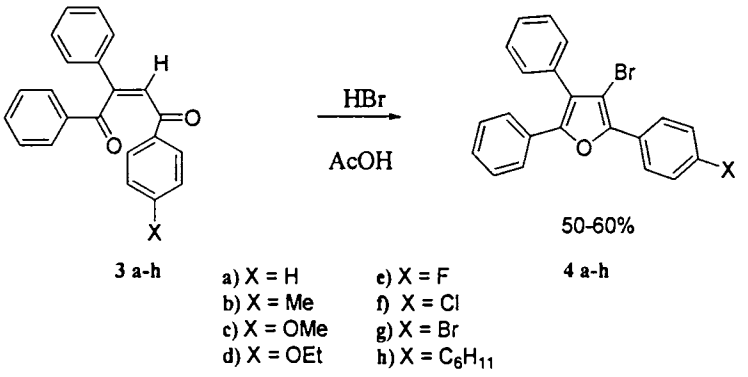
Compound *(Z)*-1,2,4-triphenyl-but-2-ene-1,4-dione **(3a)** obtained in 75% yield and showed strong IR absorptions at 1662, 1647 cm^{-1} due to the two carbonyl groups in the compound. In the ^1H NMR spectrum, the vinylic and aromatic protons were observed as a multiplet at δ 7.3-8.0. The molecular ion peak of this compound was observed at *m/z* 312 confirming its identity. Compounds **3b-h** showed very similar spectral behavior with that of **3a**. These compounds showed the IR absorptions at ~ 1757 and ~ 1653 cm^{-1} due to the two carbonyl groups. ^1H NMR data of all these compounds were comparable and they showed acceptable mass data.

4.2.2. Synthesis of 3-Bromofurans (4a-h)

cis-Dibenzoylstyrenes undergo reductive cyclisation to yield the corresponding furans.[46-49] In this context; we synthesized few 3-bromofurans from the corresponding *cis*-dibenzoylstyrenes by treating them with HBr in acetic acid (Scheme 3). Under same conditions, the *trans*-dibenzoylstyrenes failed to react.

Conventional method for the synthesis of bromofuran involved reaction of dibenzoylalkene with HBr in acetic acid. Under these condition the yield of the product was found to be low. More over yield was found to be greatly depending on the quantity as well as purity of hydrogen bromide. Hence we employed a more

efficient and convenient method, which involved passing hydrogen bromide directly into the dibenzoylalkene dissolved in acetic acid. Hydrogen bromide was generated by the reaction of bromine with 1,2,3,4-tetrahydronaphthalene; tetralin.[50]



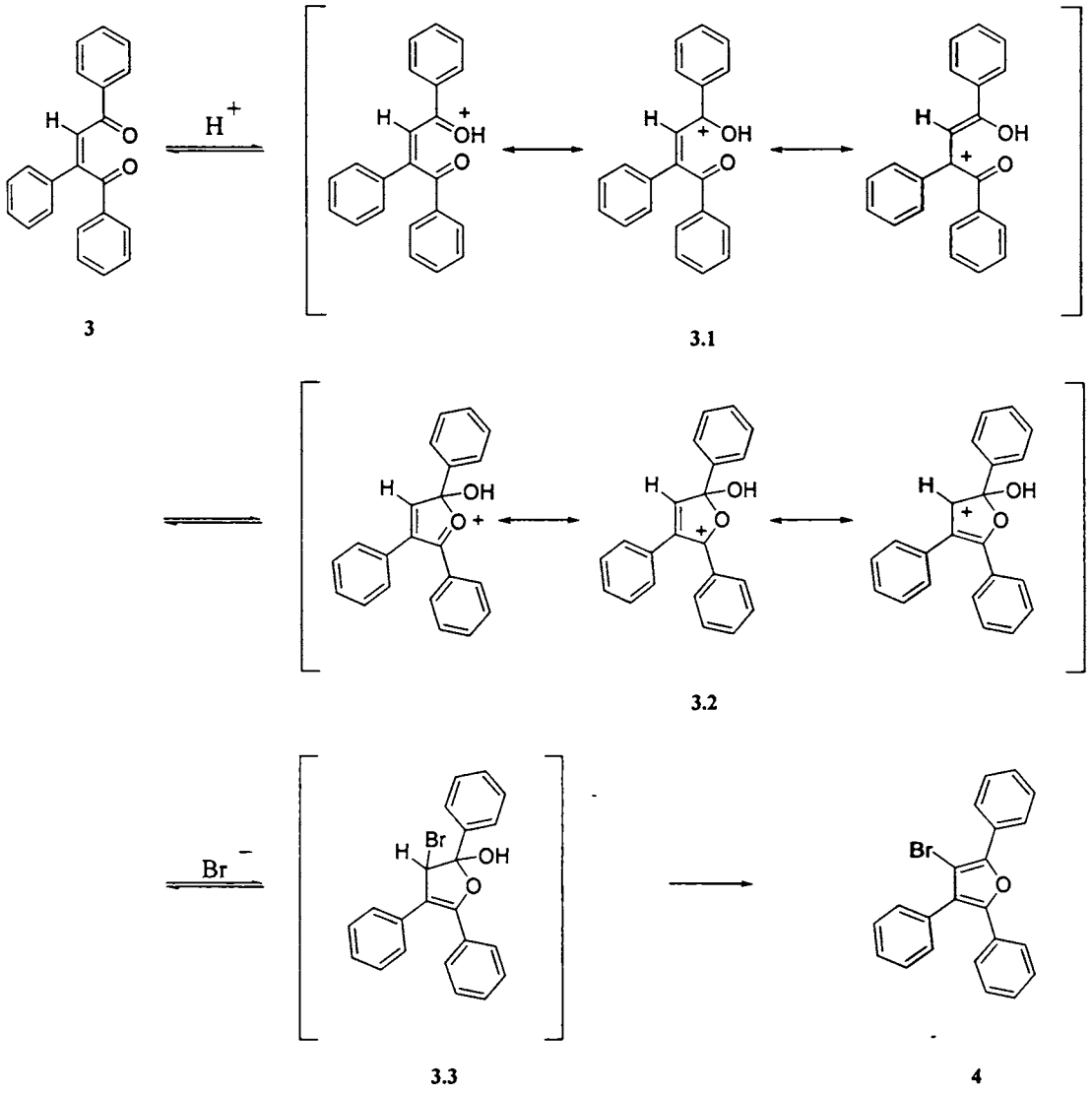
3 a-h

a) X = H
b) X = Me
c) X = OMe
d) X = OEt
e) X = F
f) X = Cl
g) X = Br
h) X = C_6H_{11}

4 a-h

Scheme 3

The greater facility of the cyclisation reactions of *cis*-dibenzoylstyrenes over the corresponding *trans*-isomers, can be explained in terms of reversible protonation of the oxygen of the α, β- unsaturated ketone system present and passage through the successive ionic intermediates which may be presumed to retain the configuration at the central ethylenic carbons[46,51,52] The two possible oxygen protonations would be affected differently by the relative effectiveness of the conjugations involving the two carbonyl groups and by electrical effects of the substituents on the central ethylenic linkage. However, regardless of relative facility of protonation, as long as configuration is maintained in the protonated state, only in the cis compounds, and not in the trans could occur facile cyclization through **3.3** intermediate to yield furan **4** (Scheme 4).



Scheme 4

Compound 3-bromo-2,4,5-triphenylfuran (**4a**) obtained in 55% yield and showed strong IR absorptions at 1265, 1066 cm^{-1} due to C-O-C asymmetric and symmetric vibrations respectively in the compound. Moreover, furan ring skeletal vibrations appeared in the range 1501-1487 cm^{-1}. In the ^1H NMR spectrum, the aromatic protons were observed as a multiplet at δ 7.2-8.0. The molecular ion peak of this compound was observed at *m/z* 375/377 further confirming its identity.

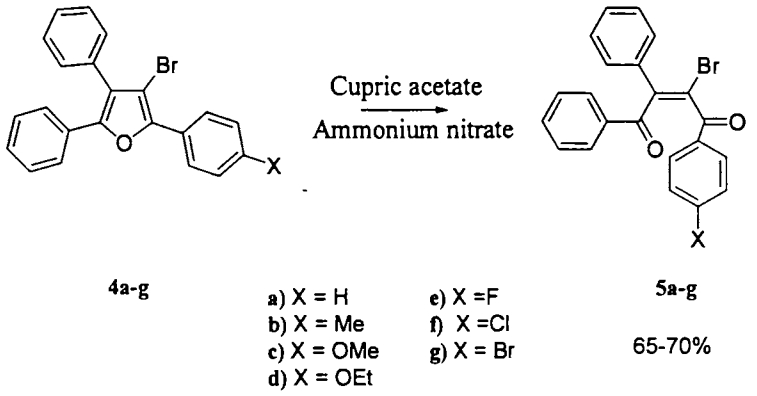
Compounds **4b-h** showed very similar spectral behaviour with those of **4a**. These compounds showed the IR absorptions at ~ 1265 and ~ 1068 cm^{-1} due to C-

O-C asymmetric and symmetric vibrations respectively in the compound and other vibrations in the range 1501- 1487 cm^{-1}. ^1H NMR data of all these compounds were comparable and these showed acceptable mass data.

4.2.3. Synthesis of *(E)*-1-Aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione (5a-g)

Following reported procedures, we synthesized bromodibenzoylstyrenes, by the oxidative cleavage of the corresponding 3-bromofurans.[52-54] Concentrated nitric acid is commonly used for the oxidation of furans. Initially, we adopted this procedure for the oxidation of 3-bromofurans. However this procedure gave mixed results with our compounds. In most cases, the yields were low and the product mixture was obtained as an intractable paste. So, we recognized the need for developing a more efficient procedure for oxidation. Based on literature precedence and our own experience,[43d] we recognized cupric acetate/ammonium nitrate as a viable alternative to nitric acid. We successfully adopted this procedure for the oxidation of 3-bromofurans. Thus, the oxidation of 4-bromofurans **4a-g** using catalytic amount of cupric acetate in the presence of stoichiometric amount of ammonium nitrate[55] produced *(E)*-1-Aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-diones **5a-g** in high yields (Scheme-4). The reaction proceeded under mild conditions and only minimal amount of undesirable side-products were formed in this case. It may be mentioned here that oxidation of all these 3-bromofurans using the new procedure developed by us also provided the corresponding unsaturated 1,4-diketones having the desired *E*-configuration. Exclusive formation of enediones having the *E*-configuration as the only product indicates that in all these instances, the reaction between cupric acetate in the presence of stoichiometric amount of ammonium nitrate and furan uniformly proceeded in a stereoselective fashion. Hence this reaction provides a simple, efficient, and more eco friendly route for the oxidation of 3-bromofuran to the corresponding 1,4-diketones in high yield and strereoselectivity. A major limitation to this procedure is illustrated in the case of **4h,** which underwent extensive decomposition under the newly developed oxidation reaction. We attribute the facile Cu(II)-catalysed oxidation of the cyclohexylphenyl component

in this molecule to the corresponding hydroperoxide to the destruction of **4h** under the conditions employed by us.[56] Structure of the enedione products **5a-g** was confirmed on the basis of spectral and analytical data (Scheme 5) .



Scheme 5

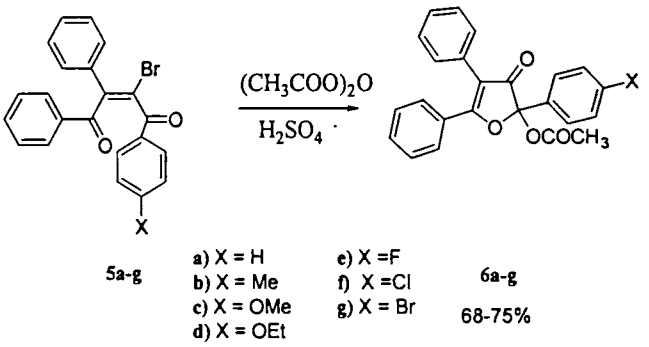
Compound *(E)*-2-bromo-1,3,4-triphenylbut-2-ene-1,4-dione (**5a)** obtained in 65% yield showed strong IR absorptions at 1666 and1651 cm^{-1} due to two carbonyl groups in the compound. In the ^1H NMR spectrum, the vinylic and aromatic protons were observed as a multiplet at δ 7.3-8.0. The molecular ion peak of this compound was observed at *m/z* 391/393 confirming its identity.

Compounds **5b-g** showed spectral behaviour very similar to those of 5a. These compounds showed the IR absorptions at ~ 1664 and ~ 1651 cm^{-1} due to two carbonyl groups. ^1H NMR data of all these compounds were comparable and the compounds showed acceptable mass data.

4.2.3. Synthesis of 2-Acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones (6a-g)

Lutz *et al* in 1954 reported the effect of configuration of bromodibenzoylstyrene on addition-cyclisation reaction in presence of acid reagents.[43,46] The E-Z pair exhibited a sharp difference in the reactivity. While acetic anhydride/sulphuric acid readily converted the isomer having the two benzoyl groups cis to each other to the corresponding furanone, the other isomer having the two benzoyl groups trans to each other was found to be unreactive. Based on this report, we synthesized the 2-Acetoxy-2-aryl-4,5-diphenyl-2H-furan-

3-ones **6a-g** by treating **5a-g** with acetic anhydride in presence of sulphuric acid (Scheme 6).



5a-g

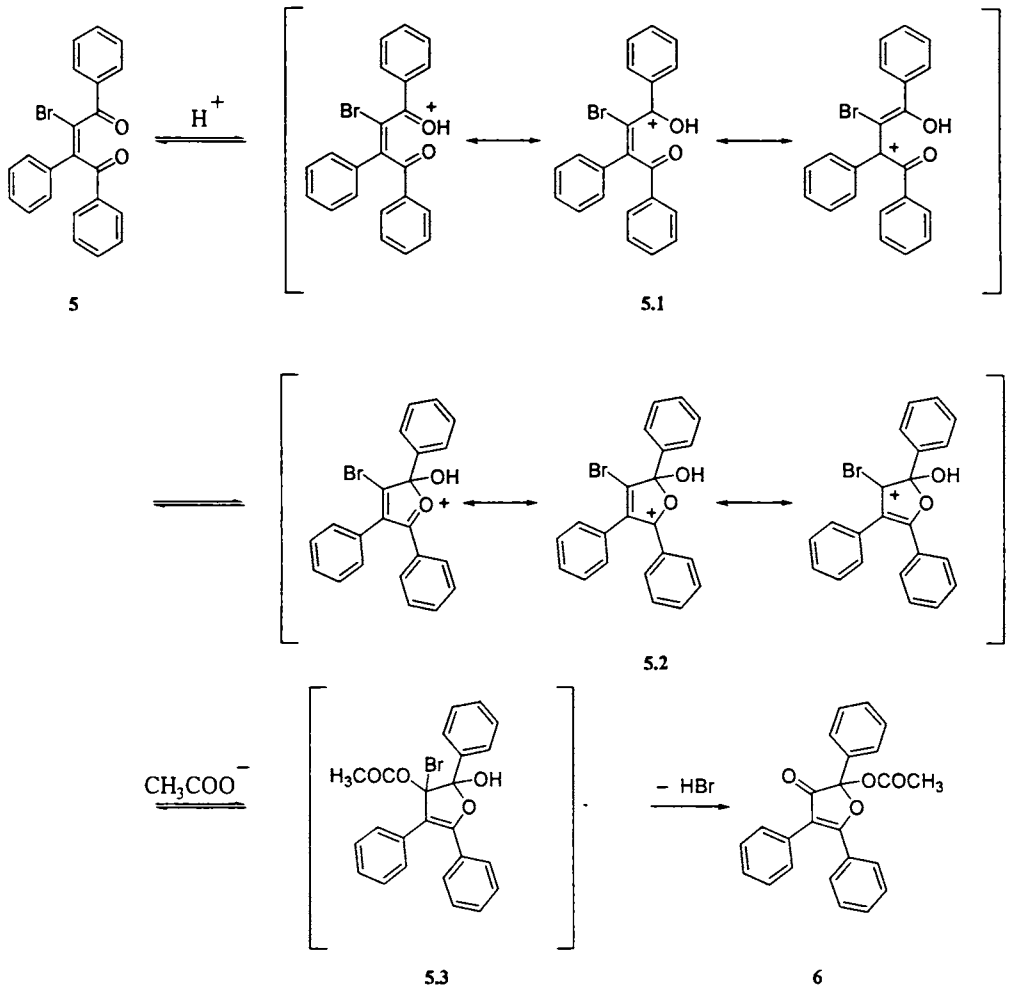
a) X = H
b) X = Me
c) X = OMe
d) X = OEt
e) X =F
f) X =Cl
g) X = Br

6a-g

68-75%

Scheme 6

The greater facility of the reactions of the cis isomers can be explained in terms of reversible protonation of the oxygens of the α,β-unsaturated ketone system. In the case of *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione due to the lack of ethylenic hydrogen to undergo dehydration, the compound underwent substitution followed by dehydrohalogenation to give corresponding furanones (Scheme 7).



Scheme 7

2-Acetoxy-2,4,5-triphenyl-2-H-furan-3-one **(6a)** which was obtained in 72% yield showed strong IR absorptions at 1771, 1716 , and 1622 cm^{-1}. In the ^1H NMR spectrum, the singlet due to CH_3 protons was observed at δ 2.2 and aromatic protons were observed as a multiplet at δ 7.3-7.8. The molecular ion peak of this compound was observed at *m/z* 370 further confirming its identity. The structure was further confirmed by elemental analysis that gave acceptable data. Similarly, 2-acetoxy-2-(4-methylphenyl)-4,5-diphenyl-2-H-furan-3-one **6b** obtained in 72% yield showed strong IR absorptions at 1772, 1714 and 1620 cm^{-1}. The compound showed a singlet at δ 2.2 corresponding to the CH_3 protons of ester group and another singlet at δ 2.37 corresponding to the three protons of the CH_3 group attached to the furanone ring system. 2-Acetoxy-2-(4-methoxyphenyl)-4,5-diphenyl-2-H-furan-3-one **6c** obtained in 70% yield showed strong IR absorptions

at 1772, 1702 and 1618 cm^{-1}. In the ^1H NMR spectrum, the compound showed singlet at δ 2.2 due to CH_3 protons, a singlet at δ 3.8 due to methoxy protons and a multiplet at δ 7.3-7.8 due to aromatic protons. 2-Acetoxy-2-(4-ethoxyphenyl)-4,5-diphenyl-2-H-furan-3-one **6d** obtained in 68% yield showed strong IR absorptions at 1772, 1704 and 1618 cm^{-1}. In the ^1H NMR spectrum singlet at δ 2.2 corresponds to CH_3 protons of ester linkage and triplet at δ 1.35 corresponds to CH_3 protons of ethoxy group. The quartet at δ 3.9 corresponds to CH_2 protons of ethoxy group and a multiplet at δ 6.9-7.8 corresponding to aromatic protons. 2-Acetoxy-2-(4-fluorophenyl)-4,5-diphenyl-2-H-furan-3-one **6e** obtained in 60% yield and showed strong IR absorptions at 1772, 1722 and 1618 cm^{-1}. The compound showed singlet at δ 2.2 due to CH_3 protons of ester group and a multiplet at δ 6.9-7.8 due to aromatic protons. 2-Acetoxy-2-(4-chlorophenyl)-4,5-diphenyl-2-H-furan-3-one **6f** obtained in 62% yield showed strong IR absorptions at 1772, 1718, 1618 cm^{-1}. The ^1H NMR spectrum showed a singlet at δ 2.2 due to CH_3 protons of ester group and a multiplet at δ 7.0-7.8 due to aromatic protons in the molecule. 2-Acetoxy-2-(4-bromophenyl)-4,5-diphenyl-2-H-furan-3-one 6g obtained in 72% yield showed strong IR absorptions at 1771, 1717 and 1624 cm^{-1}. ^1H NMR spectrum showed a singlet at δ 2.2 due to CH_3 protons of ester group and a multiplet at δ 7.0-7.8 due to aromatic protons in the molecule. The structure was further confirmed by elemental analysis that gave acceptable data.

4.3. Conclusion

In summary, 2-acetoxy-2-aryl-4,5-diphenylfuran-3-ones were synthesized by the acid catalysed cyclisation of corresponding *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione precursors. A mixture of catalytic amount of cupric acetate and ammonium nitrate was found to be an excellent reagent for the oxidative cleavage of 3-bromofurans to the corresponding *E*-isomer of 1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-diones.

4.4. Experimental

4.4.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300, 400 and 500 MHz on a Bruker FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

4.4.2. Synthesis of *(Z)*-4-Aryl-1,2-diphenyl-but-2-ene-1,4-diones(3 a-h)

4.4.2.1. *(Z)*-1,2,4-Triphenyl-but-2-ene-1,4-dione (3a). A mixture of benzil (10.500 g, 50 mmol), acetophenone (6.504 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3a**.[53]

Compound 3a: (11.700 g, 75%); mp 130 ^{0}C; IR (KBr) 1662 and 1647 (C=O), 1561 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-8.0 (m, 16H, aromatic and vinylic); MS, *m/z* 312 (M^{+}) and other peaks. Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found C, 84.48, H, 5.02.

4.4.2.2. *(Z)*-4-(4-Methylphenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3b). A mixture of benzil (10.500 g, 50 mmol), 4-methylacetophenone (7.260 g, 54.18 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was

stirred around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3b**.

Compound 3b: (11.410 g, 70%); mp 140 ^{0}C; IR (KBr) 1665 and 1653 (C=O), 1572 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 7.3-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 326 (M^+) and other peaks. Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found C, 84.32, H, 5.42.

4.4.2.3. *(Z)*-4-(4-Methoxyphenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3c). A mixture of benzil (10.500 g, 50 mmol), 4-methoxyacetophenone (8.130 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3c**.

Compound 3c: (11.115 g, 65%); mp 176 ^{0}C; IR (KBr) 2950, 2835 (O-CH_2), 1757 (C=O), 1673 and 1598 (C=C); 1250 (C-O-C asym), 1041 (C-O-C sym) cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 7.3-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 342 (M^+) and other peaks. Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found C, 80.52, H, 5.22.

4.4.2.4. *(Z)*-4-(4-Ethoxyphenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3d). A mixture of benzil (10.500 g, 50 mmol), 4-ethoxyacetophenone (8.889 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3d**.

Compound 3d: (12.816 g, 72%); mp 138-140 ^{0}C; IR (KBr) 2978, 2940 (O-CH_2), 1672 and 1657 (C=O), 1595 (C=C), 1222 (C-O-C asym), 1037 (C-O-C sym) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.1 (q, J = 7 Hz, 2H, CH_2), δ1.4 (t, J = 7 Hz, 3H, CH_3), δ 7.3-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 356 (M^+) and

other peaks. Anal. Calcd. for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found C, 80.74, H, 5.53.

4.4.2.5. *(Z)*-4-(4-Fluorophenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3e). A mixture of benzil (10.500 g, 500 mmol), 4-fluoroacetophenone (7.480 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred around at 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3e**.

Compound 3e: (10.725 g, 65%); mp 162 ^{0}C; IR (KBr) 1667 and 1651 (C=O), 1553 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 330 (M^+) and other peaks. Anal. Calcd. for $C_{22}H_{15}FO_2$: C, 79.99; H, 4.58. Found C, 79.87, H, 4.45

4.4.2.6. *(Z)*-4-(4-Chlorophenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3f). A mixture of benzil (10.500 g, 50 mmol), 4-chloroacetophenone (8.347 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3f.**

Compound 3f: (12.975 g, 75%); mp 180 ^{0}C; IR (KBr) 1666 and 1651 (C=O), 1589 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 346 (M^+), 348 (M^++2) and other peaks. Anal. Calcd. for $C_{22}H_{15}ClO_2$: C, 76.19; H, 4.36. Found C, 76.05, H, 4.42.

4.4.2.7. *(Z)*-4-(4-Bromophenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3g). A mixture of benzil (10.500 g, 50 mmol), 4-bromoacetophenone (10.786 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3g**.

Compound 3g: (13.685 g, 70%); mp 208 ^{0}C; IR (KBr) 1664 and 1652 (C=O), 1599 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 15H, aromatic and vinylic).

4.4.2.8. *(Z)*-4-(4-Cyclohexylphenyl)-1,2-diphenyl-but-2-ene-1,4-dione (3h). A mixture of benzil (10.500 g, 50 mmol), 4-cyclohexylacetophenone (10.948 g, 54.2 mmol) and powdered potassium hydroxide (2.000 g) in methanol (60 mL) was stirred at around 60 ^{0}C for 1 h and later kept in refrigerator for 48 h. The light yellow solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **3h**.

Compound 3h: (13.199 g, 67%); mp 180 ^{0}C; IR (KBr) 1675 and 1651 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (m, 6H, CH_2), δ 1.6 (m, 4H, CH_2), δ 2.6 (m, 1H, CH), δ 7.3-8.0 (m, 15H, aromatic and vinylic); MS, *m/z* 394 (M^+) and other peaks. Anal. Calcd. for $C_{28}H_{26}O_2$: C, 85.25; H, 6.64. Found C, 85.18, H, 6.56.

4.4.3. Synthesis of 2-Aryl-3-bromo-4,5-diphenylfuran (4a-h)

4.4.3.1. 3-Bromo-2,4,5-triphenylfuran (4a). A solution of **3a** (9.360 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4a**.

Compound 4a: (6.188 g, 55%); mp 128 ^{0}C; IR (KBr) 3057, 3031, 3000 (aromatic C-H stretch), 1600, 1500 (C=C ring stretch), 1265 (C-O-C asym.) and 1066 (C-O-C sym.) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-8.0 (m, 15H, aromatic); MS, *m/z* 375 (M^+), 377 (M^++2) and other peaks. Anal. Calcd. for $C_{22}H_{15}BrO$: C, 70.41; H, 4.03. Found C, 70.35, H, 4.08.

4.4.3.2. 3-Bromo-2-(4-methylphenyl)-4,5-diphenylfuran (4b). A solution of **3b** (9.780 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4b**.

Compound 4b: (7.936 g, 68%); mp 134 ^{0}C; IR (KBr) 3060, 3031, 3000 (aromatic C-H stretch), 2918, 2857 (methyl C-H stretch), 1600, 1495 (C=C ring stretch), 1265 (C-O-C asym.) and 1068 (C-O-C sym.) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3) δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{23}H_{17}BrO$: C, 70.96; H, 4.40. Found C, 70.85, H, 4.32.

4.4.3.3. 3-Bromo-2-(4-methoxyphenyl)-4,5-diphenylfuran (4c). A solution of **3c** (10.260 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4c**.

Compound 4c: (6.683 g, 55%); mp 151 ^{0}C; IR (KBr) 3060, 3036, 2995 (aromatic C-H stretch), 2962, 2833 (methyl C-H stretch), 1601, 1500 (C=C ring stretch), 1257 (C-O-C asym.) and 1070 (C-O-C sym.), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 7.2-8.0 (m, 14H, aromatic); MS, *m/z* 405 (M^+), 407 (M^++2) and other peaks. Anal. Calcd. for $C_{23}H_{17}BrO_2$: C, 68.16; H, 4.23. Found C, 68.10, H, 4.17.

4.4.3.4. 3-Bromo-2-(4-ethoxyphenyl)-4,5-diphenylfuran (4d). A solution of **3d** (10.680 g 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4d**.

Compound 4d: (5.657 g, 45%); mp 155 ^{0}C; IR (KBr) 3057, 3036, 2995 (aromatic C-H stretch), 1601, 1500 (C=C ring stretch), 1255 (C-O-C asym.) and 1071 (C-O-C sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.9 (quartet, 2H, CH_2), δ 1.35 (triplet, 3H, CH_3), δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{24}H_{19}BrO_2$: C, 68.75; H, 4.57. Found C, 68.69, H, 4.51.

4.4.3.5. 3-Bromo-2-(4-fluorophenyl)-4,5-diphenylfuran (4e). A solution of **3e** (9.900 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4e**.

Compound 4e: (5.895 g, 50%); mp 125 ^{0}C; IR (KBr) 3060, 3034 (aromatic C-H stretch), 1601, 1501 (C=C ring stretch), 1255 (C-O-C asym.) and 1068 (C-O-C sym.) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{22}H_{14}BrFO$: C, 67.19; H, 3.59. Found C, 67.02, H, 3.49.

4.4.3.6. 3-Bromo-2-(4-chlorophenyl)-4,5-diphenylfuran (4f). A solution of **3f** (10.380 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4f**.

Compound 4f: (7.362 g, 60%); mp 127 ^{0}C; IR (KBr) 3060, 3036, 2995 (aromatic C-H stretch), 1601, 1499 (C=C ring stretch), 1248 (C-O-C asym.) and 1068 (C-O-C sym.) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{22}H_{14}BrClO$: C, 64.49; H, 3.44. Found C, 64.37, H, 3.39.

4.4.3.7. 3-Bromo-2-(4-bromophenyl)-4,5-diphenylfuran (4g). A solution of **3g** (11.730 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The white solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4g**.

Compound 4g: (7.491 g, 55%); mp 157 ^{0}C; IR (KBr) 3057, 3028, 3000 (aromatic C-H stretch), 1600, 1498 (C=C ring stretch), 1260 (C-O-C asym.) and 1067 (C-O-C sym.) cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{22}H_{14}Br_2O$: C, 58.18; H, 3.11. Found C, 58.02, H, 3.17.

4.4.3.8. 3-Bromo-2-(4-cyclohexylphenyl)-4,5-diphenylfuran (4h). A solution of **3h** (11.820 g, 30 mmol) in acetic acid (100 mL) was treated with HBr gas for 2 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (1:1) of methanol and chloroform to give **4h**.

Compound 4h: (6.992 g, 51%); mp 157 ^{0}C; IR (KBr) 3064, 3022 (aromatic C-H stretch), 1601, 1499 (C=C ring stretch), 1261 (C-O-C asym.) and 1069 (C-O-C sym.); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.3 (m, 6H, CH_2), δ 1.6 (m, 4H, CH_2), δ 2.6 (m, 1H, CH), δ 7.2-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{28}H_{25}BrO$: C, 73.52; H, 5.51. Found C, 73.46, H, 5.47.

4.4.4. Synthesis of *(E)*-1-Aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione (5 a-g)

4.4.4.1. *(E)*-2-Bromo-1,3,4-triphenylbut-2-ene-1,4-dione (5a). Cupric acetate (0.027 g, 0.15 mmol), ammonium nitrate (1.328 g, 16.6 mmol), **4a** (5.000g, 13.3 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5a**.

Compound 5a: (3.380 g, 65%); mp 110 ^{0}C; IR (KBr) 1666 and 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-8.0 (m, 15H, aromatic); MS, *m/z* 391 (M^+), 393 (M^++2) and other peaks. Anal. Calcd. for $C_{22}H_{15}BrO_2$: C, 67.53; H, 3.86. Found C, 67.42, H, 3.75.

4.4.4.2. *(E)*-2-Bromo-1-(4-methylphenyl)-3,4-diphenylbut-2-ene-1,4-dione (5b). Cupric acetate (0.026 g, 0.14 mmol), ammonium nitrate (1.288 g, 16.1mmol), **4b** (5.000 g, 12.9 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5b**.

Compound 5b: (3.435 g, 66%); mp 125 ^{0}C; IR (KBr) 1664 and 1651 (C=O), 1601(C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 7.25-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{23}H_{17}BrO_2$: C, 68.16; H, 4.23. Found C, 68.02, H, 4.28.

4.4.4.3. *(E)*-2-Bromo-1-(4-methoxyphenyl)-3,4-diphenylbut-2-ene-1,4-dione (5c). Cupric acetate (0.025 g, 0.14 mmol), ammonium nitrate (1.232 g, 15.4mmol), **4c** (5.000 g, 12.35 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5c**.

Compound 5c: (3.380 g, 65%); mp120 ^{0}C; IR (KBr) 2950, 2835 (O-CH_2), 1660 and 1652 (C=O), 1598(C=C), 1250 (C-O-C asym), 1041 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 7.25-8.0 (m, 14H, aromatic); MS, *m/z* 421 (M^+), 423 (M^++2) and other peaks. Anal. Calcd. for $C_{23}H_{17}BrO_3$: C, 65.57; H, 4.07. Found C, 65.42, H, 3.98.

4.4.4.4. *(E)*-2-Bromo-1-(4-ethoxyphenyl)3,4-diphenylbut-2-ene-1,4-dione (5d). Cupric acetate (0.024 g, 0.13 mmol), ammonium nitrate (1.192 g, 14.9mmol), **4d** (5.000 g, 11.9 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5d**.

Compound 5d: (3.468 g, 67%); mp 130 ^{0}C; IR (KBr) 2978, 2940 (O-CH_2), 1660 and 1652 (C=O), 1222 (C-O-C asym), 1037 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.9 (quartet, 2H, CH_2), δ1.35 (triplet, 3H, CH_3), δ 7.25-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{24}H_{19}BrO_3$: C, 66.22; H, 4.40. Found C, 66.13, H, 4.34.

4.4.4.5. *(E)*-2-Bromo-1-(4-fluorophenyl)-3,4-diphenylbut-2-ene-1,4-dione (5e). Cupric acetate (0.025 g, 0.14 mmol), ammonium nitrate (1.272 g, 15.9 mmol), **4e** (5.000 g, 12.7 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was

observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5e**.

Compound 5e: (3.428 g, 66%); mp 121 ^{0}C; IR (KBr) 1676 and 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{22}H_{14}BrO_2$: C, 64.57; H, 3.45. Found C, 64.45, H, 3.50.

4.4.4.6. *(E)*-2-Bromo-1-(4-chlorophenyl)3,4-diphenylbut-2-ene-1,4-dione (5f). Cupric acetate (0.024g, 0.13 mmol), ammonium nitrate (1.220 g, 15.25 mmol), **4f** (5.000 g, 12.2 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5f**.

Compound 5f: (3.526 g, 68%); mp 126 ^{0}C; IR (KBr) 1674 and 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 14H, aromatic). Anal. Calcd. for $C_{22}H_{14}BrClO_2$: C, 62.07; H, 3.31. Found C, 61.98, H, 3.24.

4.4.4.7. *(E)*-2-Bromo-1-(4-bromophenyl)3,4-diphenylbut-2-ene-1,4-dione (5g). Cupric acetate (0.026 g, 0.14 mmol), ammonium nitrate (1.32 g, 16.5 mmol), **4g** (6.000 g, 13.2 mmol) and 10 mL of 80% aqueous acetic acid were taken in a 100 mL round bottom flask with a water condenser. The mixture was heated with occasional shaking for 90 minutes. A vigorous evolution of nitrogen was observed. The light yellow solid separated was collected by filtration and recrystallised from methanol to yield **5g**.

Compound 5g: (4.095 g, 66%); mp 124 ^{0}C; IR (KBr) 1670 and 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-8.0 (m, 14H, aromatic); MS, *m/z* 470 (M^+), 472 (M^++2) and other peaks. Anal. Calcd. for $C_{22}H_{14}Br_2O_2$: C, 56.20; H, 3.00. Found C, 56.13, H, 2.94.

4.4.5. Synthesis of 2-Acetoxy-2-aryl-4,5-diphenylfuran-3-one (6 a-g)

4.4.5.1. 2-Acetoxy-2,4,5-triphenyl-2-H-furan-3-one (6a). Six drops of Conc. sulphuric acid were added to a solution of **5a** (3.000 g, 7.7 mmol) in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid of **6a**.

Compounds 6a: (2.051 g, 72%); mp 132 ^{0}C; IR (KBr) 1771(O-CO) 1716 (C=O) and 1622 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 7.3 - 7.8 (m, 15H, aromatic); ^{13} C (NMR, 300 MHz, $CDCl_3$) δ 21.1 (CH_3); 100.6 (C), 115.4 (CH), 126 (CH), 129.1 (CH), 130.0 (CH), 132.6 (C), 134.0 (C), 168.6 (CH), 176.7 (CO), 197.0 (CO), MS, *m/z* 370 (M^+) and other peaks. Anal. Calcd. for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found C, 77.76, H, 4.84.

4.4.5.2. 2-Acetoxy-2-(4-methylphenyl)-4,5-diphenyl-2-H-furan-3-one (6b). Six drops of Conc.sulphuric acid were added to a solution of **5b** (3.250 g, 8.0 mmol) in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6b**.

Compound 6b: (2.212 g; 72%); mp 132 ^{0}C; IR (KBr) 1772 (O-CO), 1714 (C=O) and 1620 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 2.37 (s, 3H, CH_3), δ 7.3-7.8 (m, 14H, aromatic); 13 C (500 MHz) δ 20.0 (CH_3); 100.0 (C), 125.8 (CH), 115 (CH), 128 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.3 (CH), 129.4 (CH), 130.1 (CH), 132.2 (C), 140.0 (C), 167.8 (C), 176.0 (CO), 196.9 (CO); MS, *m/z* 384 (M^+) and other peaks. Anal. Calcd. for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found C, 77.68, H, 5.53.

4.4.5.3. 2-Acetoxy-2-(4-methoxyphenyl)-4,5-diphenyl-2-H-furan-3-one (6c). Six drops of Conc.sulphuric acid were added to a solution of 3.400 g (8.1 mmol) of **5c** in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6c**.

Compound 6c: (2.268 g, 70%); mp 131 ^{0}C; IR (KBr) 1772 (O-CO), 1702 (C=O) and 1618 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 3.8 (s, 3H, OCH_3), δ 7-7.8 (m, 14H, aromatic); MS, *m/z* 400 (M^+) and other peaks. Anal. Calcd. for $C_{25}H_{20}O_5$: C, 74.99; H, 5.03. Found C, 74.78, H, 5.53.

4.4.5.4. 2-Acetoxy-2-(4-ethoxyphenyl)-4,5-diphenyl-2-H-furan-3-one (6d). Six drops of Concd. sulphuric acid were added to a solution of 3.500 g (8.0 mmol)of **5d** in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6d.**

Compound 6d: (2.252 g, 68%); mp 130 ^{0}C. IR (KBr) 1772 (O-CO), 1704 (C=O) and 1618 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.35 (triplet, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 3.9 (quartet, 2H, CH_2), δ 6.9-7.8 (m, 14H, aromatic); MS, *m/z* 414 (M^+). Anal. Calcd. for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35. Found C, 74.64, H, 5.81.

4.4.5.5. 2-Acetoxy-2-(4-fluorophenyl)-4,5-diphenyl-2-H-furan-3-one (6e). Six drops of Conc.sulphuric acid were added to a solution of 3.300 g (8.1 mmol) of **5e** in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6e**.

Compound 6e: (1.886 g; 60%); mp 132 ^{0}C; IR (KBr) 1772 (O-CO), 1722 (C=O) and 1618 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 6.9-7.8 (m, 14H, aromatic). Anal. Calcd. for $C_{24}H_{17}FO_4$: C, 74.22; H, 4.41. Found C, 73.64, H, 4.81.

4.4.5.6. 2-Acetoxy-2-(4-chlorophenyl)-4,5-diphenyl-2-H-furan-3-one (6f). Six drops of Conc.sulphuric acid were added to a solution of 3.400 g (8 mmol) of **5f** in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6f.**

Compound 6f: (2.004 g, 62%); mp 134 ^{0}C; IR (KBr) 1772 (O-CO), 1718 (C=O) and 1618 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 7.0-7.8 (m, 14H, aromatic). Anal. Calcd. for $C_{24}H_{17}ClO_4$: C, 71.20; H, 4.23. Found C, 70.80, H, 4.74.

4.4.5.7. 2-Acetoxy-2-(4-bromophenyl)-4,5-diphenyl-2-H-furan-3-one (6g). Six drops of Conc.sulphuric acid were added to a solution of 3.800 g (8.1 mmol) of **5g** in 30 mL acetic anhydride. The mixture was allowed to stand for fifteen minutes at room temperature and then poured into excess of water. Crystallisation of the product from isopropanol gave light yellow solid **6g**.

Compound 6g: (2.619 g, 72%); mp 135 ^{0}C; IR (KBr) 1771 (O-CO), 1717 (C=O) and 1624 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), δ 7.0-7.8 (m, 14H, aromatic). Anal. Calcd. for $C_{24}H_{17}BrO_4$: C, 64.16; H, 3.81. Found C, 63.96, H, 3.94.

4.5. X-ray Crystallographic Analyses of 6a

The crystal was grown in a mixture (3:2) of chloroform and methanol. A single crystal of suitable size (0.29 x 0.24 x 0.21 mm^3) of the compound was mounted on glass fibers under a nitrogen atmosphere. X-ray data were collected on a Bruker SMART charge coupled device (CCD) detector system at low temperature. Graphite-monochromated Mo Kα radiation was supplied by a sealed-tube X-ray source. Structure solution and refinement were carried out using the SHELXTL-PLUS software package (PC version).[54] The remaining non-hydrogen atoms were found by successive full-matrix least-squares refinement and difference Fourier map calculations. In general, non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed at idealized positions and assumed the riding model.[55]

The compound **6a** crystallizes into an orthorhombic lattice with a non-centrosymmetric space group $P2_12_12_1$. There are four crystallographically unique molecules of **6a** in the asymmetric unit. The molecular structure showing 30%

displacement ellipsoids with atomic-numbering scheme is shown in Figure 1. The molecular packing of the molecule in a unit cell is shown in Figure 2.

Table 1. Crystal data and structure refinement for compound 6a

Identification code	p11904/lt	
Empirical formula	$C_{24}H_{18}O_4$	
Formula weight	370.38	
Temperature	165(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.5570(2) Å	α= 90°.
	b = 12.0871(2) Å	β= 90°.
	c = 15.0728(3) Å	γ = 90°.
Volume	1923.34(6) $Å^3$	
Z	4	
Density (calculated)	1.279 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	776	
Crystal size	0.29 x 0.24 x 0.21 mm^3	
Theta range for data collection	2.36 to 28.31°.	
Index ranges	$-14\leq h\leq 14$, $-16\leq k\leq 16$, $-20\leq l\leq 19$	
Reflections collected	31278	
Independent reflections	4765 [R(int) = 0.034]	
Completeness to theta = 28.31°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9820 and 0.9753	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4765 / 0 / 254	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0789	
R indices (all data)	R1 = 0.0452, wR2 = 0.0818	
Absolute structure parameter	0.5(7)	
Largest diff. peak and hole	0.148 and -0.154 $e.Å^{-3}$	

Table 2. Bond angles (in degrees) of compound 6a

C(4)-O(1)-C(1)	*108.02(9)*	*C(7)-C(8)-C(9)*	*119.99(14)*
C(11)-O(2)-C(1)	117.93(10)	C(8)-C(9)-C(10)	120.32(14)
O(2)-C(1)-O(1)	110.01(10)	C(9)-C(10)-C(5)	119.62(14)
O(2)-C(1)-C(5)	107.01(10)	O(3)-C(11)-O(2)	122.83(13)
O(1)-C(1)-C(5)	110.99(10)	O(3)-C(11)-C(12)	127.44(14)
O(2)-C(1)-C(2)	114.77(11)	O(2)-C(11)-C(12)	109.72(13)
O(1)-C(1)-C(2)	104.23(10)	C(14)-C(13)-C(18)	119.19(13)
C(5)-C(1)-C(2)	109.88(10)	C(14)-C(13)-C(3)	120.89(13)
O(4)-C(2)-C(3)	130.73(13)	C(18)-C(13)-C(3)	119.80(12)
O(4)-C(2)-C(1)	124.03(12)	C(13)-C(14)-C(15)	120.08(16)
C(3)-C(2)-C(1)	105.10(10)	C(16)-C(15)-C(14)	120.33(17)
C(4)-C(3)-C(2)	107.10(11)	C(17)-C(16)-C(15)	120.14(15)
C(4)-C(3)-C(13)	130.44(12)	C(16)-C(17)-C(18)	120.11(16)
C(2)-C(3)-C(13)	122.45(11)	C(13)-C(18)-C(17)	120.14(14)
C(3)-C(4)-O(1)	114.15(11)	C(20)-C(19)-C(24)	119.17(12)
C(3)-C(4)-C(19)	132.34(12)	C(20)-C(19)-C(4)	120.86(11)
O(1)-C(4)-C(19)	113.51(10)	C(24)-C(19)-C(4)	119.97(11)
C(6)-C(5)-C(10)	120.03(12)	C(21)-C(20)-C(19)	120.32(13)
C(6)-C(5)-C(1)	121.45(12)	C(20)-C(21)-C(22)	120.01(13)
C(10)-C(5)-C(1)	118.39(12)	C(23)-C(22)-C(21)	120.05(13)
C(5)-C(6)-C(7)	119.90(14)	C(24)-C(23)-C(22)	120.34(13)
C(8)-C(7)-C(6)	120.12(15)	C(23)-C(24)-C(19)	120.08(12)

Table 3. Bond lengths(in angstroms) of compound 6a

O(1)-C(4)	1.3780(15)	C(8)-C(9)	1.381(2)
O(1)-C(1)	1.4299(15)	C(9)-C(10)	1.386(2)
O(2)-C(11)	1.3723(16)	C(11)-C(12)	1.493(2)
O(2)-C(1)	1.4142(15)	C(13)-C(14)	1.386(2)
O(3)-C(11)	1.1948(17)	C(13)-C(18)	1.3891(19)
O(4)-C(2)	1.2117(16)	C(14)-C(15)	1.391(2)
C(1)-C(5)	1.5153(18)	C(15)-C(16)	1.374(3)
C(1)-C(2)	1.5475(19)	C(16)-C(17)	1.372(3)
C(2)-C(3)	1.4502(18)	C(17)-C(18)	1.394(2)
C(3)-C(4)	1.3561(18)	C(19)-C(20)	1.3976(18)
C(3)-C(13)	1.4831(18)	C(19)-C(24)	1.3996(17)
C(4)-C(19)	1.4631(17)	C(20)-C(21)	1.3834(19)
C(5)-C(6)	1.381(2)	C(21)-C(22)	1.388(2)
C(5)-C(10)	1.3884(19)	C(22)-C(23)	1.385(2)
C(6)-C(7)	1.390(2)	C(23)-C(24)	1.3820(19)
C(7)-C(8)	1.377(2)		

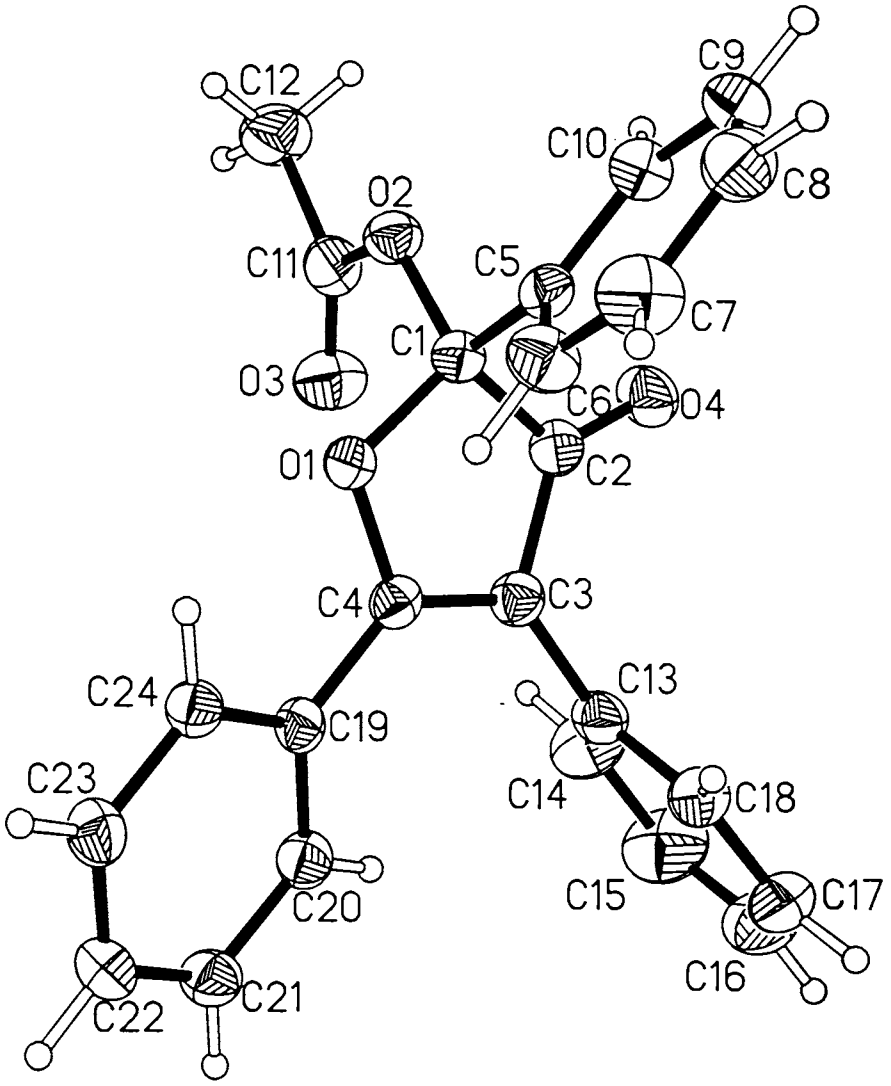


Figure 1. ORTEP diagram of molecular structure of compound 6a in the crystal

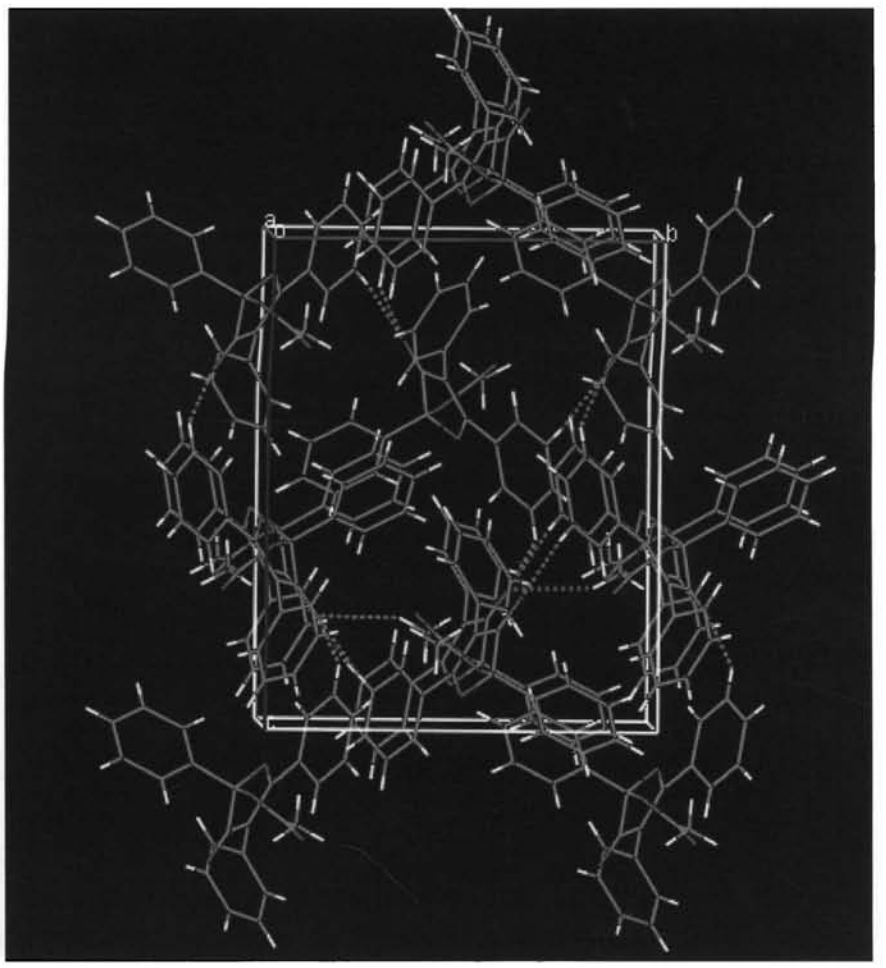


Figure 2. Molecular packing of 6a down b-axis

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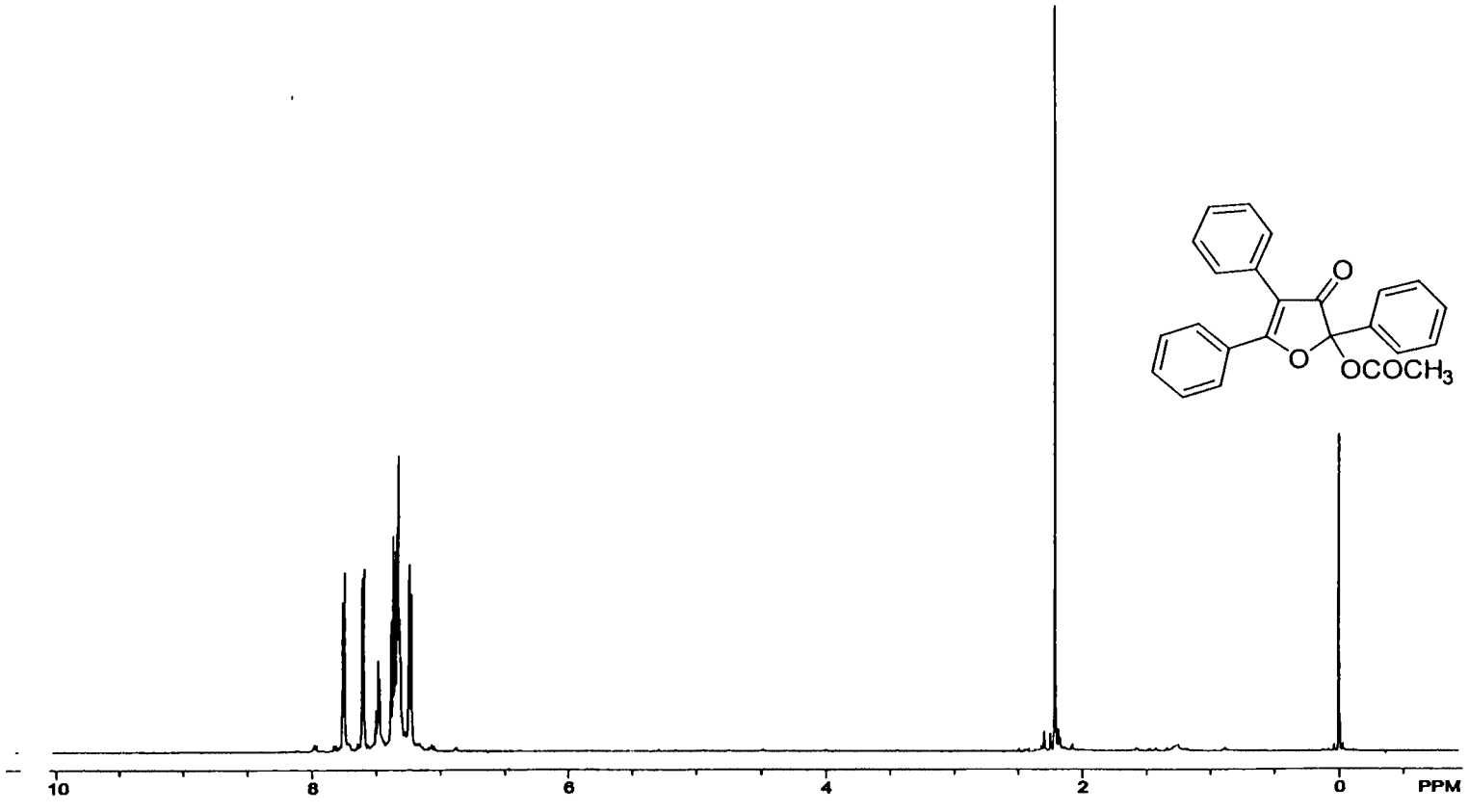


Figure 3. ^{1}H NMR Spectrum of Compound 6a

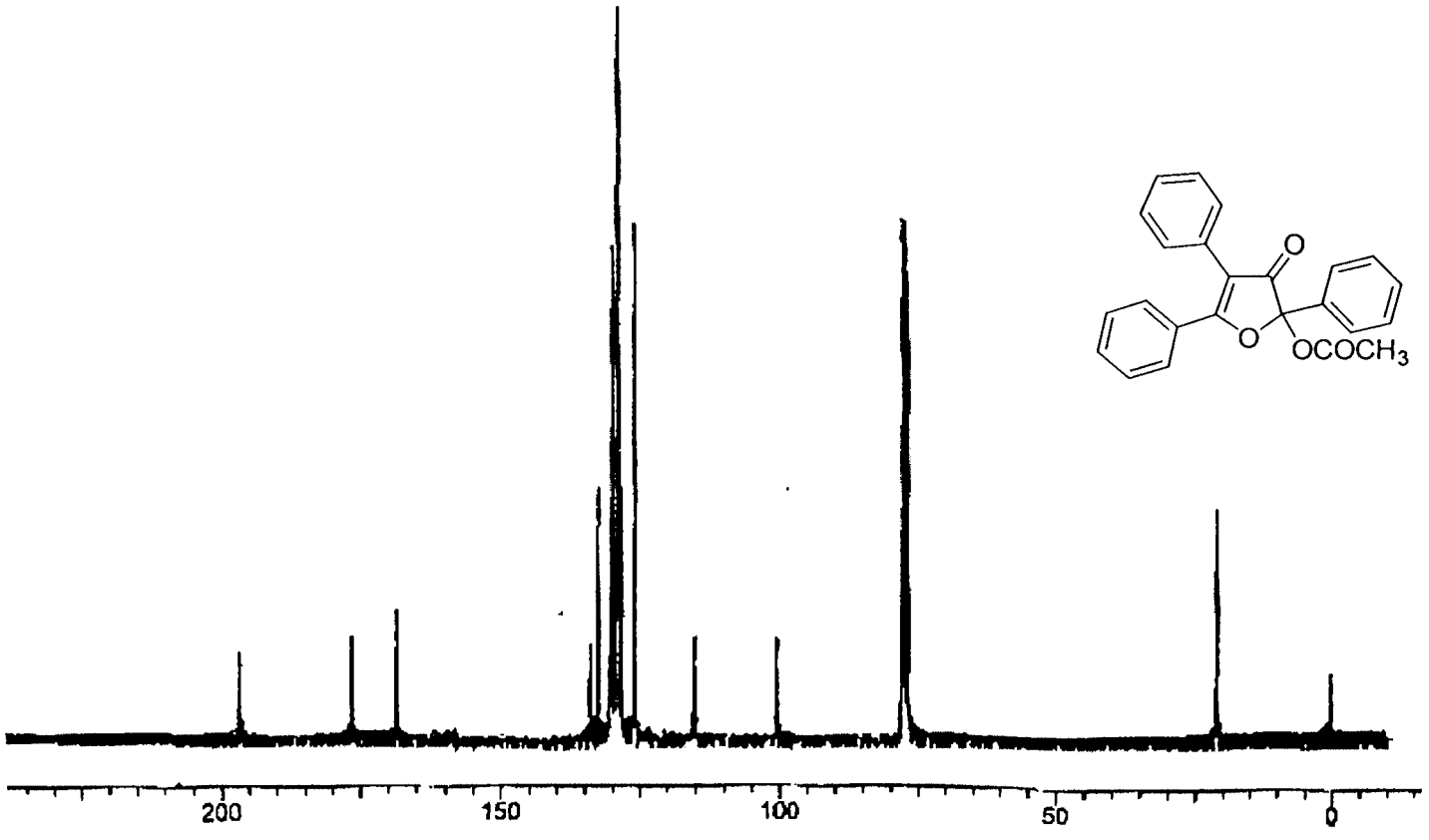


Figure 4. ^{13}C NMR Spectrum of Compound 6a

Chapter-5

SYNTHESIS OF 2-ARYL-2-METHOXY-4,5-DIPHENYL-2H-FURAN-3-ONES

2-Methoxy-3(2H)-furanones can be conveniently prepared by treating *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione with methanol saturated with hydrogen chloride gas. Our endeavors on the synthesis of a few 2-aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones from the corresponding *(E)*-bromodibenzoylalkenes is discussed in this chapter.

5.1 Introduction

In the previous chapter we have described the simple and facile route for the synthesis of 3(2H)-furanones from dibenzoylalkene precursors.[1,2] Since the synthesis and original establishment of the structure of 2-acetoxy 3(2H)-furanones, there has been a continued interest in the synthesis of another series of 3(2H)-furanone by introducing a methoxy substituent at 2- position of the furanone ring.

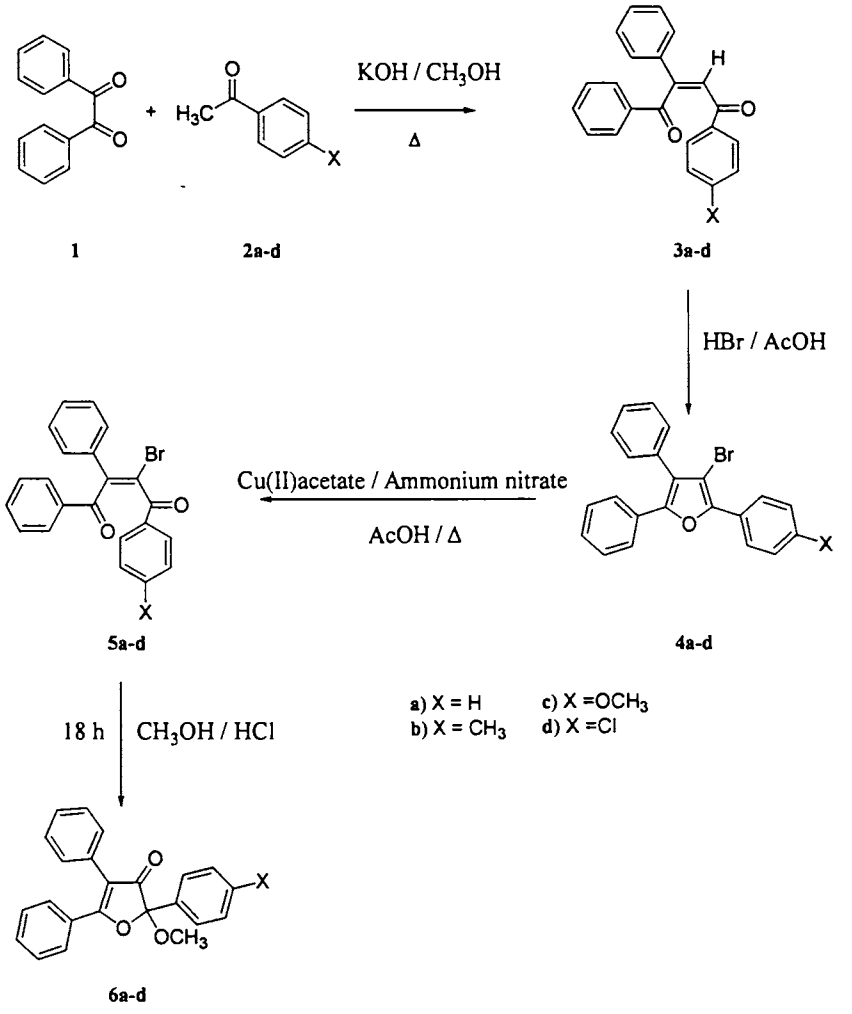
We identified *(E)*-bromodibenzoylalkenes as appropriate synthetic precursors for the synthesis of our target molecules. *(E)*-bromodibenzoylalkenes on reaction with methanol saturated with hydrogen chloride gas gave 2-aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones in good yield.[2]

5.2. Results and Discussion

5.2.1. Synthesis of 2-Aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones (6a-d)

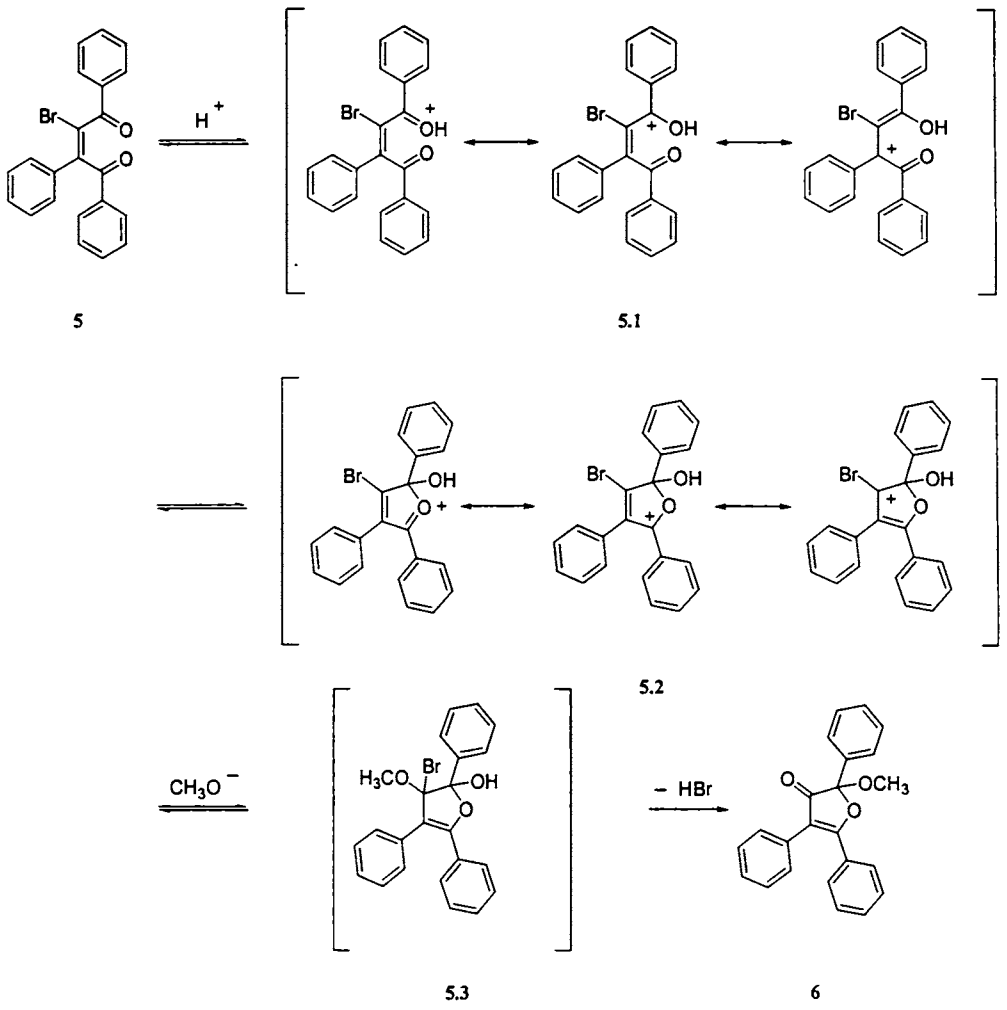
2-Aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones **(6a-d)** were synthesised from *(Z)*-dibenzoylstyrene precursors. The overall reaction sequence involves the synthesis of *(Z)*-dibenzoylstyrenes by Claisen-Schmidt condensation of benzil with suitably substituted acetophenones[3-6] followed by acid catalysed cyclisation to yield 3-bromofurans[2,5,6] which in turn undergoes oxidative cleavage in presence of cupric acetate-ammonium nitrate[7] to give *(E)*-bromodibenzoylalkenes.[2,8] These

(E)-bromodibenzoylalkenes on reaction with methanol saturated with hydrogen chloride yield corresponding 2-methoxy-3(2H)-furanones[2] (**6a-d**). The overall reaction sequence is depicted in Scheme 1.



Scheme 1

The reaction mechanism can be explained in terms of the reversible protonation of the carbonyl oxygen of α, β- unsaturated ketone system which lack an ethylenic hydrogen, and passage through successive ionic intermediates[1,2] (Scheme 2).



Scheme 2

The compound 2-methoxy-2,4,5-triphenyl-2H-furan-3-one **(6a)** which was obtained in 50% yield showed strong IR absorptions at 1671, 1596 , 1228, and 1038 cm^{-1}. In the ^1H NMR spectrum, the singlet due to OCH_3 protons was observed at δ 3.5 and aromatic protons were observed as a multiplet at δ 7.2-7.8. The molecular ion peak of this compound was observed at *m/z* 342 further confirming its identity. The structure was further confirmed by elemental analysis that gave acceptable data.

Compounds **6b**, **6c** and **6d** showed similar spectral data to that of **6a**. The ^1H NMR of all these three compounds showed a singlet at δ 3.5 indicating the presence of a methoxy group in the molecule. IR spectra showed carbonyl and ethylinic absorptions around 1700 and 1604 cm^{-1} respectively. Elemental as well

as mass spectral analyses further confirmed their identity as 2-aryl-2-methoxy-4,5-diphenylfuran-3-ones.

5.3. Conclusion

In summary 2-aryl-2-methoxy-4,5-diphenylfuran-3-ones **(6a-d)** could be synthesized in good yields by the acid catalysed cyclisation of corresponding *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione precursors.

5.4. Experimental

5.4.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

5.4.2. Starting Materials

Synthesis of *(Z)*-4-aryl-1,2-diphenyl-but-2-ene-1,4-diones **(3a-d),** 2-aryl-3-bromo-4,5-diphenylfuran **(4a-d)** and *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione **(5a-d)** is given in Chapter 4.

5.4.3. Synthesis of 2-Aryl-2-methoxy-4,5-diphenyl-2H-furan-3-ones (6a-d)

5.4.3.1. 2-Methoxy-2,4,5-triphenyl-2H-furan-3-one (6a). A solution of **5a** (3.000 g, 7.7 mmol) in 70 mL of methanol saturated with hydrogen chloride was allowed to stand for 18 hours in a glass stoppered flask at room temperature. The mixture was poured into excess of water and the solid that separated out was collected by filtration. Crystallisation of the product from *2*-propanol gave **6a** as a light yellow solid.

Compound 6a: (1.318 g, 50%); mp 145 ^{0}C; IR (KBr) 2937, 2841 (methyl C-H), 1808 (C=C), 1671 (C=O), 1596 (C=C), 1228 (C-O-C asym) and 1038 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.5 (s, 3H, OCH_3), δ 7.2-7.8 (m, 15H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.77 (OCH_3), 104.38 (C), 126.14 (CH), 127.96 (CH), 128.61 (CH), 128.71 (CH), 129.07 (CH), 129.15 (CH), 129.53 (CH), 132.59 (CH), 134.38 (C), 176.58 (C), 197 (CO); MS, *m/z* 342(M^+) and other peaks; Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found C, 80.50, H, 5.42.

5.4.3.2. 2-Methoxy-2-(4-methylphenyl)-4,5-diphenyl-2H-furan-3-one (6b). A solution of **5b** (3.000 g, 7.4 mmol) in 70 mL of methanol saturated with hydrogen chloride was allowed to stand for 18 hours in a glass stoppered flask at room temperature. The mixture was poured into excess of water and the solid that separated out was collected by filtration. Crystallisation of the product from *2*-propanol gave **6b** as a light yellow solid.

Compound 6b: (1.398 g, 53%); mp 140 ^{0}C; IR (KBr) 2964, 2935, 2831 (methyl C-H), 1807 (C=C), 1712 (C=O), 1602 (C=C), 1226 (C-O-C asym.) and 1028 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 3.5 (s, 3H, OCH_3), δ 7.2-7.8 (m, 14H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.78 (CH_3), 52.22 (OCH_3), 105.20 (C), 125.74 (CH), 128.18 (CH), 132.03 (C), 139.08 (C), 178.00 (C), 198.25 (CO); MS, *m/z* 356 (M^+) and other peaks; Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found C, 80.68, H, 5.73.

5.4.3.3. 2-Methoxy-2-(4-methoxyphenyl)-4,5-diphenyl-2H-furan-3-one (6c). A solution of **5c** (3.000 g 7.1 mmol) in 70 mL of methanol saturated with

hydrogen chloride was allowed to stand for 18 hours in a glass stoppered flask at room temperature. The mixture was poured into excess of water and the solid that separated out was collected by filtration. Crystallisation of the product from *2*-propanol gave **6c** as light yellow solid.

Compound 6c: (1.347 g, 51%) mp 166 ^{0}C; IR (KBr) 2937, 2841 (methyl C-H), 1779 (C=C), 1703 (C=O), 1613 (C=C), 1253 (C-O-C asym) and 1022 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.5 (s, 3H, OCH_3), δ 3.8 (s, 3H, OCH_3), δ 7-7.8 (m, 14H, aromatic); MS, *m/z* 372 (M^+) and other peaks; Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found C, 76.78, H, 5.64.

5.4.3.4. 2-(4-Chlorophenyl)-2-methoxy-4,5-diphenyl-2H-furan-3-one (6d). A solution of **5d** (3.000 g 7.1 mmol) in 70 mL of methanol saturated with hydrogen chloride was allowed to stand for 18 hours in a glass stoppered flask at room temperature. The mixture was poured into excess of water and the solid that separated out was collected by filtration. Crystallisation of the product from *2*-propanol gave **6d** as a light yellow solid.

Compound 6d: (1.468 g, 55%); mp 148 ^{0}C; IR (KBr), 2841 (methyl C-H), 1804 (C=C), 1710 (C=O), 1604 (C=C), 1230 (C-O-C asym), and 1038 (C-O-C sym) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.5 (s, 3H, OCH_3), δ 7.2-7.8 (m, 14H, aromatic). Anal. Calcd for $C_{23}H_{17}ClO_3$: C, 73.31; H, 4.55. Found C, 73.10, H, 4.64.

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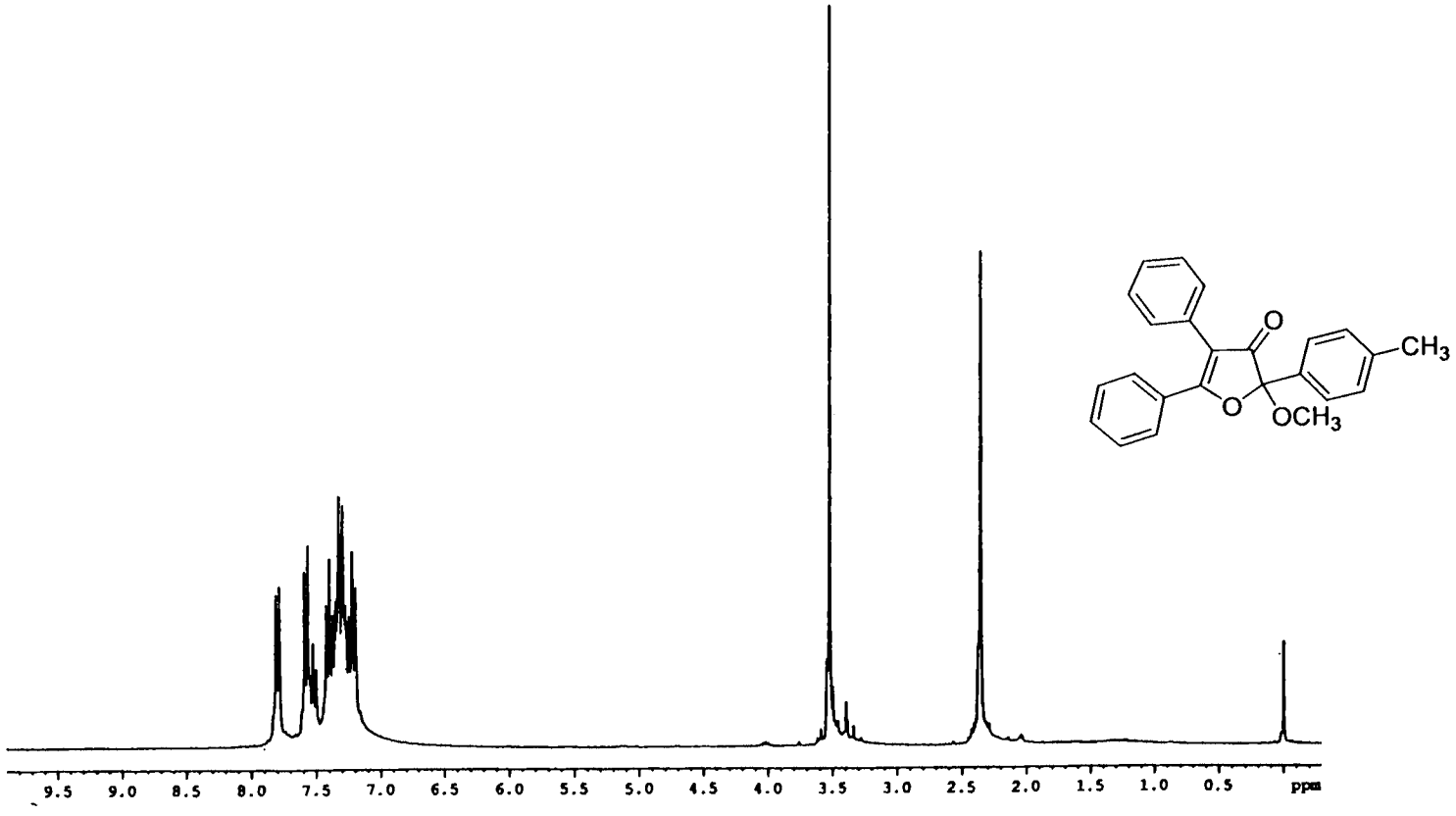


Figure 1. ^{1}H NMR Spectrum of Compound 6b

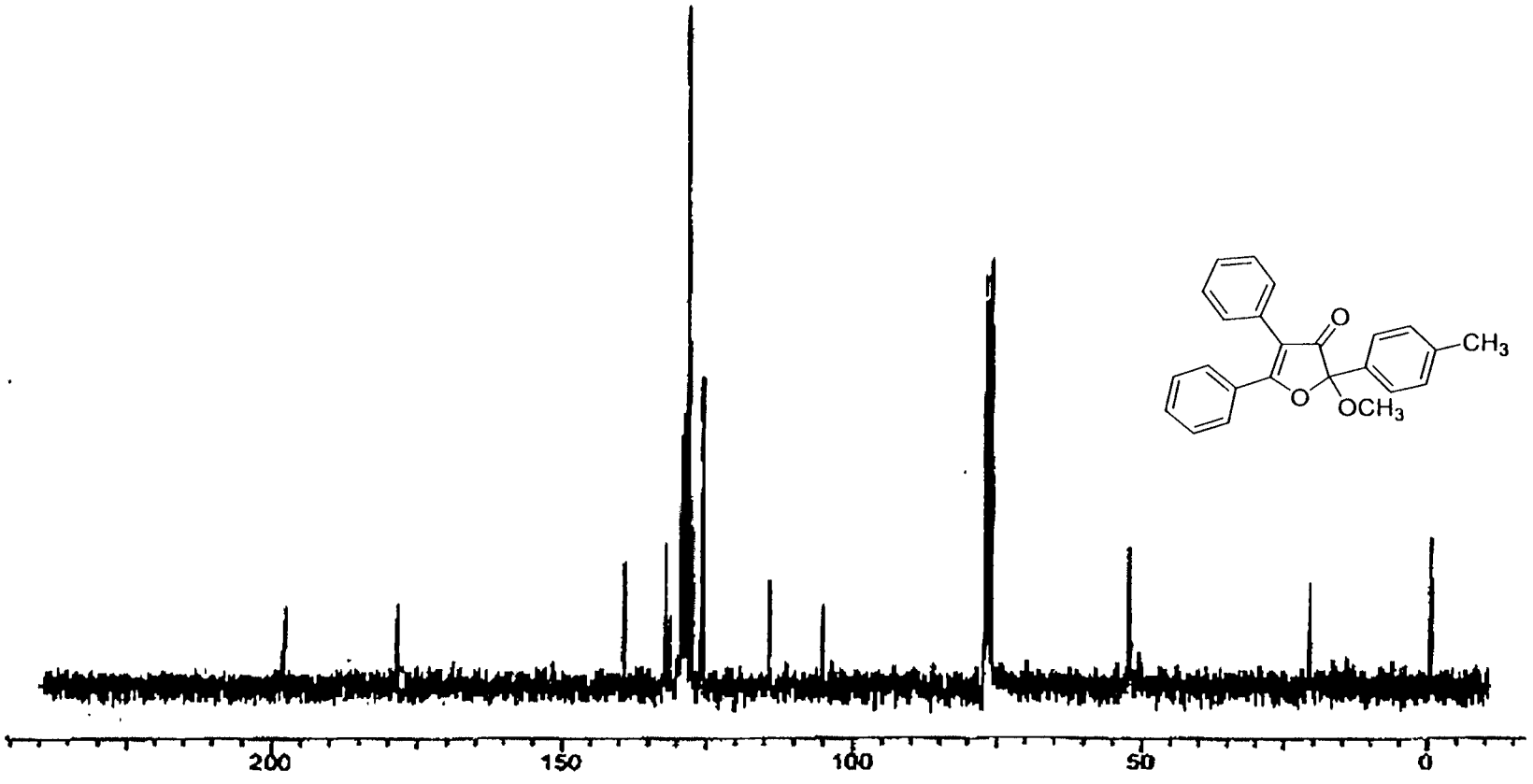


Figure 2. ^{13}C Spectrum of Compound 6b

Chapter-6

SYNTHESIS OF 2-ARYL-2-CHLORO-4,5-DIPHENYL-2H-FURAN-3-ONES

(E)-Bromodibenzoylalkenes on reaction with acetyl chloride in presence of catalytic amount of concentrated sulphuric acid yield 2-chloro-3(2H)-furanones. This chapter presents the syntheses of several 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones from the corresponding bromodibenzoylalkene precursors.

6.1. Introduction

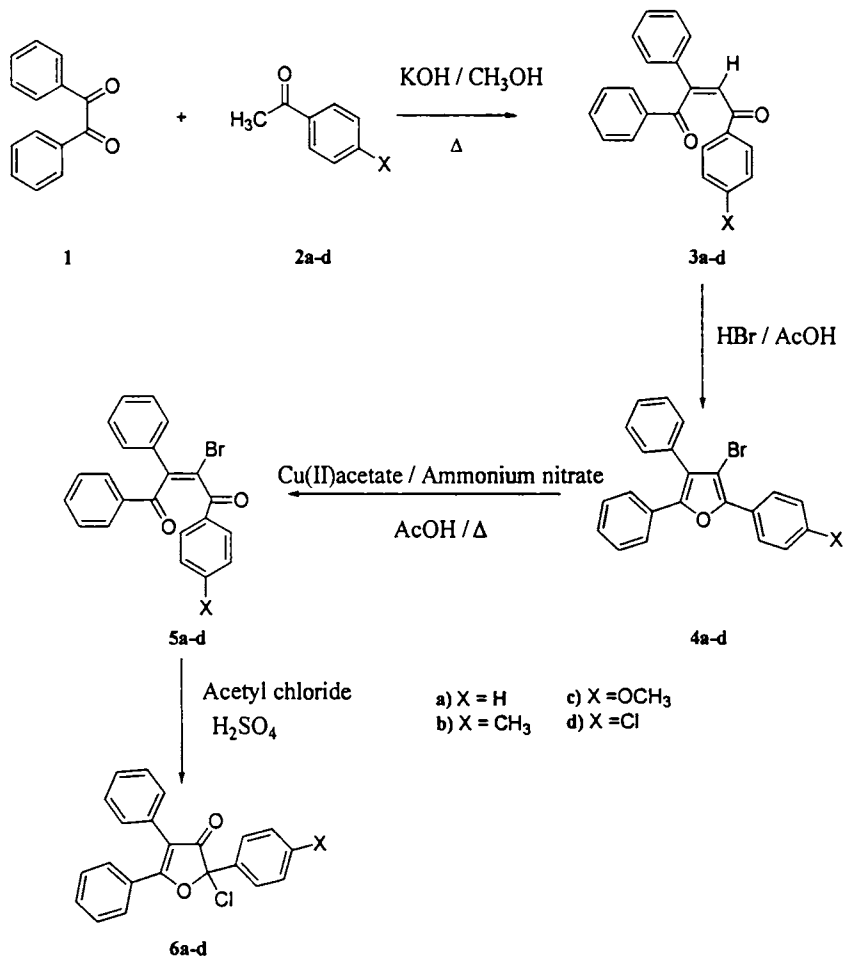
Our persisting interest in the chemistry of 3(2H)-furanones[1] encouraged us to synthesis yet another class of 3(2H)-furanones by varying the substituent at the 2-position of the furanone ring.[2] Thus, in conjunction with our studies on furanones, we synthesized 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones from dibenzoylalkene precursors [2-5].

(Z)-Dibenzoylalkenes[3-6] undergo acid-catalysed cyclisation to yield 3-bromofurans,[2,5-7] which on oxidative cleavage gives corresponding *E*-bromodibenzoylalkenes.[2,8,9] These bromodibenzoylalkenes are converted to suitably substituted 2-chloro-3(2H)-furanones on treatment with acetyl chloride in the presence of sulphuric acid.[2,7]

6.2. Results and Discussion

The overall synthetic sequence for syntheses of 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones from the corresponding bromodibenzoylalkene precursors is shown in Scheme 1. We prepared the desired 2H-furan-3-one derivatives adopting a four-step synthetic sequence. A series of *Z*-dibenzoylstyrenes were prepared by the base-catalysed condensation between benzil and suitably substituted acetophenones. Upon treatment with hydrogen bromide in acetic acid, these dibenzoylstyrenes underwent a domino acid-catalysed cyclisation-dehydration-substitution sequence to yield the corresponding 3-

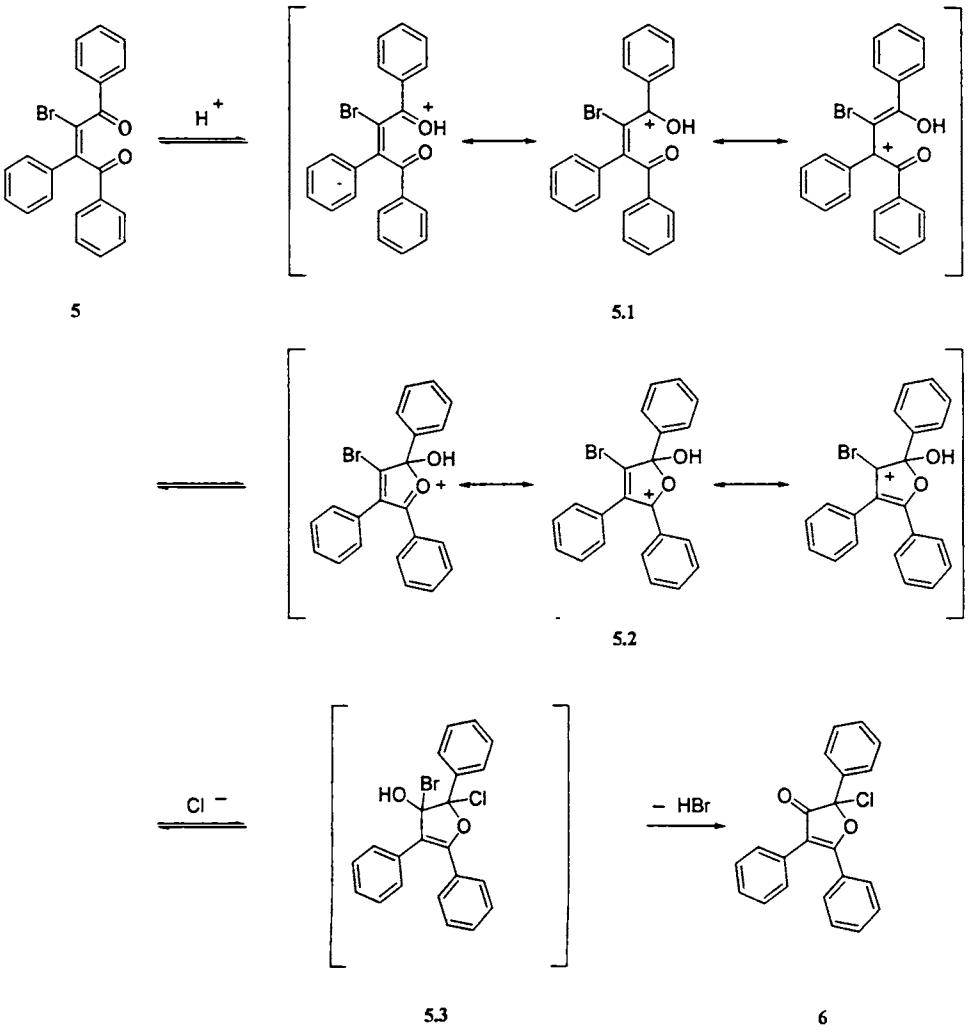
bromofurans. Using the novel cupric acetate/ammonium nitrate-mediated oxidation procedure developed by us, we oxidized the bromofurans stereoselectively to the corresponding bromodibenzoylstyrenes having the E-configuration. The bromodibenzoylstyrenes could be conveniently converted to the desired chloro-substituted 3(2H)-furanones by the action of acetyl chloride in the presence of catalytic amounts of concentrated sulphuric acid. It may be noted here that the initial steps involved in the synthetic sequence are identical to those adopted for the synthesis of 2-acetoxy-2-aryl-4,5-diphenyl-2H-furan-3-ones described in Chapter 4 of this thesis.



Scheme 1

The mechanism for the conversion of bromodibenzoylstyrenes **5a-d** in presence of acetyl choride and catalytic amount of sulphuric acid to the corresponding 2-chlorofuranones **6a-d** may be explained in term of the pathways

indicated in Scheme 2. The reaction proceeds through the reversible protonation of the oxygen of the α, β- unsaturated ketone system and its passage through successive ionic intermediates **5.1** and **5.2**.



5 5.1 5.2 5.3 6

Scheme 2

The compound 2-chloro-2,4,5-triphenyl-2H-furan-3-one **(6a)** was obtained in 42% yield and showed strong IR absorptions at 1698 and 1602 cm^{-1}. In the ^1H NMR spectrum, the aromatic protons were observed as a multiplet at δ 7.2-7.8. The molecular ion peak of this compound was observed at *m/z* 346 further confirming its identity. The structure was further confirmed by elemental analysis that gave acceptable data.

Compounds **6b**, **6c** and **6d** showed similar spectral behaviour like **6a**. These compounds also showed the IR absorptions at ~ 1700 and ~1603 cm^{-1} due to the carbonyl and ethylenic groups respectively. The ^{1}H NMR spectra of all these compounds were comparable and showed acceptable analysis and mass data. Therefore these compounds were confirmed as 2-aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones.

6.3. Conclusion

In summary 2-aryl-2-chloro-4,5-diphenylfuran-3-ones **6a-d** could be synthesized in moderate yield by the acid-catalysed cyclisation of corresponding *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione precursors.

6.4. Experimental

6.4.1. General procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infrared spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Bruker FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

6.4.2. Starting Materials

Synthesis and characterization of *(Z)*-4-aryl-1,2-diphenyl-but-2-ene-1,4-diones **(3a-d)**, 2-aryl-3-bromo-4,5-diphenylfuran **(4a-d)** and *(E)*-1-aryl-2-bromo-3,4-diphenylbut-2-ene-1,4-dione **(5a-d)** are described in Chapter 4 of this thesis.

6.4.3. Synthesis of 2-Aryl-2-chloro-4,5-diphenyl-2H-furan-3-ones (6a-d)

6.4.3.1. 2-Chloro-2,4,5-triphenyl-2-H-furan-3-one 6a. Four drops of conc. sulphuric acid were added to a solution of **5a** (2.000 g, 5.1 mmol) in 19.6 mL acetyl chloride. The mixture was allowed to stand for fifteen minutes at room temperature and was poured into excess of water. The light yellow solid separated was collected by filtration and recrystallised from isopropanol to yield **6a**.

Compound 6a: (0.741 g, 42%); mp 224 ^{0}C; IR (KBr) 1698 (C=O) and 1602 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.8 (m, aromatic); MS, *m/z* 346 (M^+), 348 (M^++2) and other peaks. Anal. Calcd for $C_{22}H_{15}ClO_2$: C, 76.19; H, 4.36. Found C, 76.50, H, 4.28.

6.4.3.2. 2-Chloro-2-(4-methylphenyl)-4,5-diphenyl-2H-furan-3-one (6b). Four drops of conc. sulphuric acid were added to a solution of **5b** (2.000 g, 4.9 mmol) in 19.6 mL acetyl chloride. The mixture was allowed to stand for fifteen minutes at room temperature and was poured into excess of water. The light yellow solid separated was collected by filtration and recrystallised from isopropanol to yield **6b**.

Compound 6b: (0.794 g, 45%); mp 228 ^{0}C; IR (KBr) 3063, 2918 (methyl C-H), 1693 (C=O) and 1603 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, CH_3), δ 7.2-7.8 (m, 14H, aromatic); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.3 (CH_3), 102.1 (C), 125.6 (CH), 127.9 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 129.4 (C), 129.6 (C), 132.6 (C), 133.0 (C), 139.7 (C), 179.1 (C), 198.2 (CO); MS, *m/z* 360 (M^+), 362 (M^++2) and other peaks. Anal. Calcd for $C_{23}H_{17}ClO_2$ C, 76.56; H, 4.75. Found C, 76.68, H, 4.53.

6.4.3.3. 2-Chloro-2-(4-methoxyphenyl)-4,5-diphenyl-2H-furan-3-one (6c). Four drops of conc. sulphuric acid were added to a solution of **5b** (2.000 g, 4.8 mmol) in 19.6 mL acetyl chloride. The mixture was allowed to stand for fifteen minutes at room temperature and was poured into excess of water. The light yellow solid separated was collected by filtration and recrystallised from isopropanol to yield **6c**.

Compound 6c: (0.776 g, 43%); mp 224-226 ^{0}C; IR (KBr) 1618 (C=C), 1701 (C=O), 1253 (C-O-C asymmetric stretching), 1072 (C-O-C symmetric stretching) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, OCH_3), δ 7.2-7.9 (m, 14H, aromatic); MS, *m/z* 376 (M^+), 378 (M^++2) and other peaks. Anal. Calcd for $C_{23}H_{17}ClO_3$: C, 73.31; H, 4.55. Found C, 73.08, H, 4.62.

6.4.3.4. 2-Chloro-2-(4-chlorophenyl)-4,5-diphenyl-2H-furan-3-one (6d). Four drops of conc. sulphuric acid were added to a solution of **5d** (2.000 g, 4.7 mmol) in 19.6 mL acetyl chloride. The mixture was allowed to stand for fifteen minutes at room temperature and was poured into excess of water. The light yellow solid separated was collected by filtration and recrystallised from isopropanol to yield **6d**.

Compound 6d: (0.752 g, 42%); mp 225-228 ^{0}C; IR (KBr) 1604 (C=C) and 1695 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.8 (m, 14 H, aromatic). Anal. Calcd for $C_{22}H_{14}Cl_2O_2$: C, 69.31; H, 3.70. Found C, 70.80, H, 3.54.

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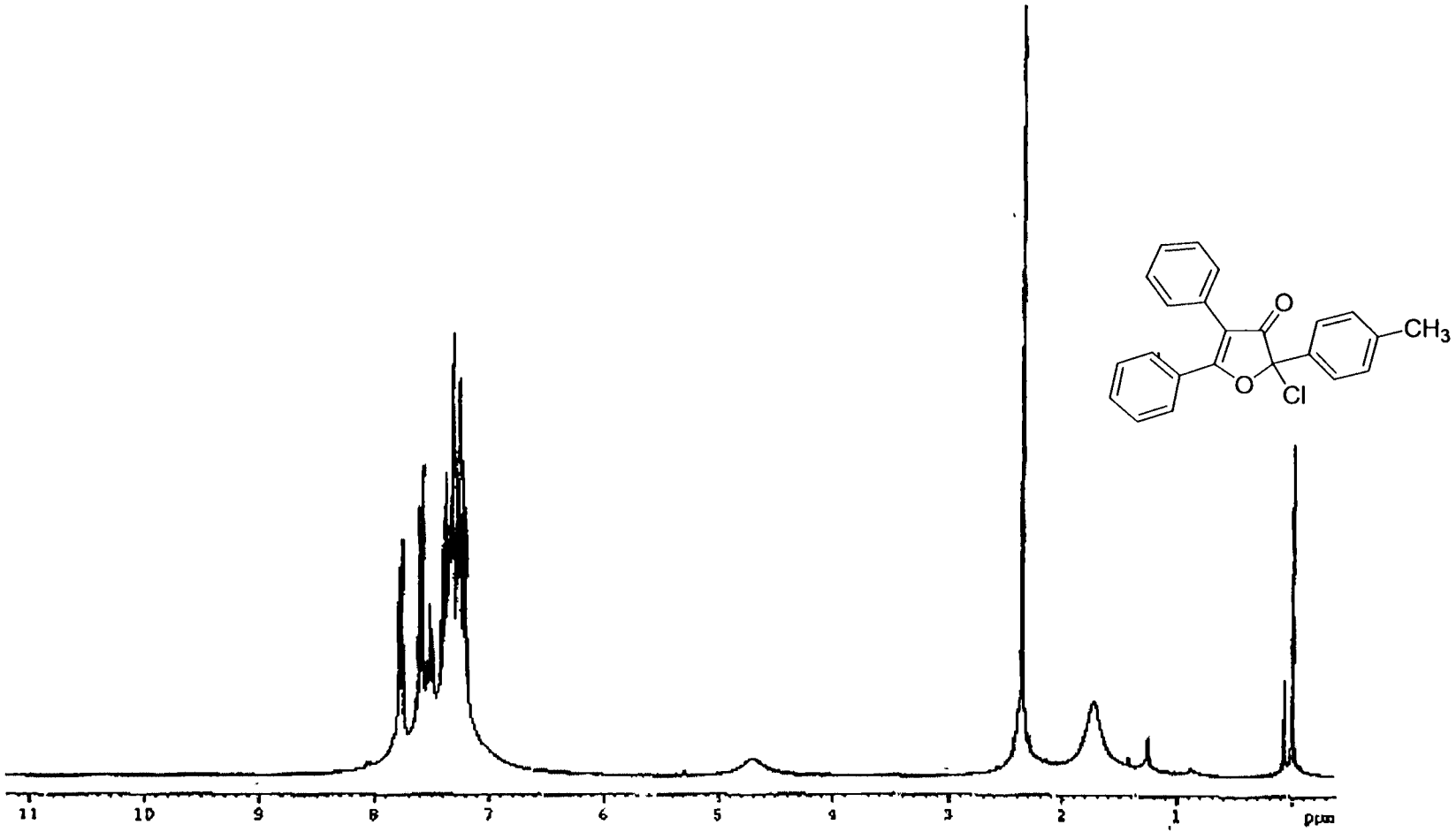


Figure 1. ^{1}H NMR Spectrum of Compound 6b

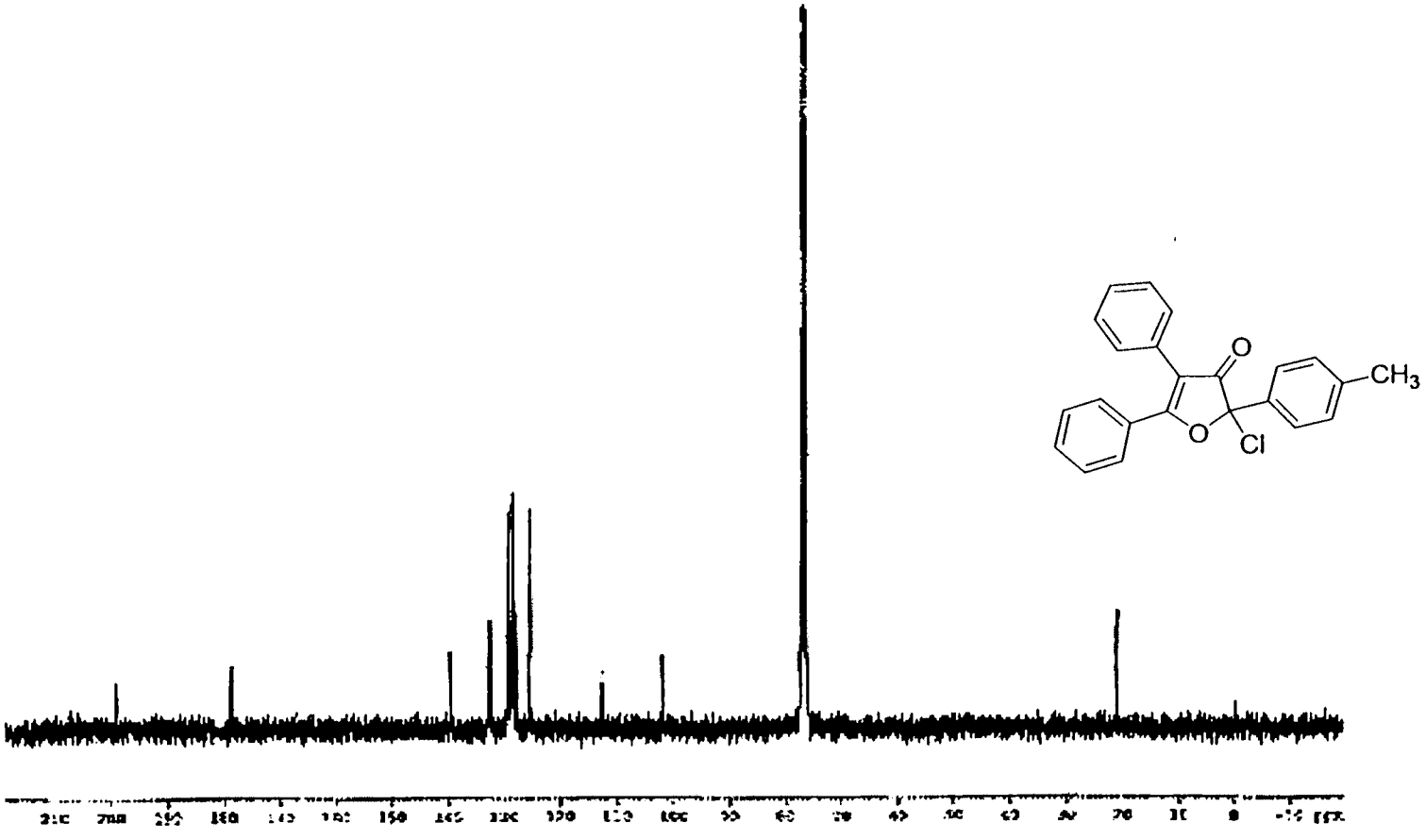


Figure 2. ^{13}C NMR Spectrum of Compound 6b

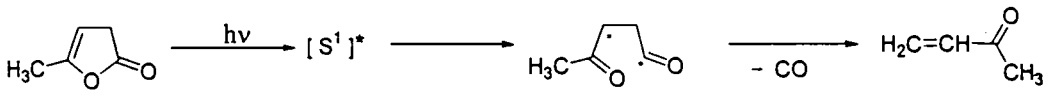
Chapter 7

PHOTOCHEMICAL TRANSFORMATIONS OF 3,3-BIS(4-CHLOROPHENYL)-5-ARYL-3H-FURAN-2-ONES

Photochemical transformations of few 3,3-bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones were studied. On direct irradiation these aryl substituted 2(3H)-furanones underwent decarbonylation to yield corresponding α,β-unsaturated carbonyl compounds and upon sensitised irradiation they underwent dimersation arising through a 2+2 cycloaddition reaction.

7.1. Introduction

Photochemical transformations of several 2(3H)-furanones have been investigated in detail. It has been reported that unsaturated lactones undergo a variety of phototransformations such as decarbonylation,[1-4,15] decarboxylation,[5] solvent addition to double bonds,[6-8] migration of aryl substituents [9-11] and dimerisation.[11-13] Upon irradiation, α-Angelica lactone (**1**), for example, is converted to methyl vinyl ketone (**3**) (Scheme 1).[1] Chapman and McIntosh have noted that the critical requirement for clean photochemical cleavage of the acyl-oxygen bond is the presence of a double bond adjacent to the ether oxygen.[3] Stabilisation of the incipient oxy radical was considered to be a determining factor in the photo-cleavage of the bond.

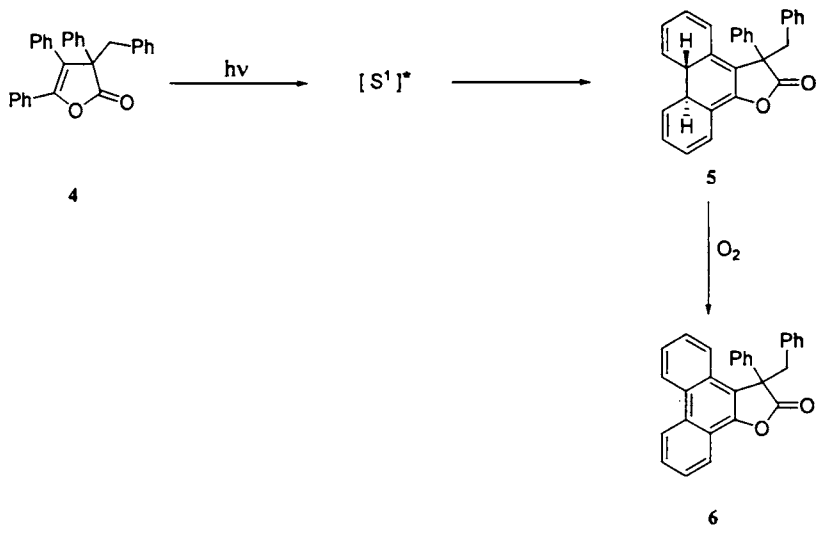


1 2 3

Scheme 1

Photochemical transformation of 2(3H)-furanones containing a benzyl group at the third position has also been studied.[10] On direct irradiation in benzene and methanol, 3-benzyl-3,4,5-triphenyl-3H-furan-2-one (**4**) gave the corresponding

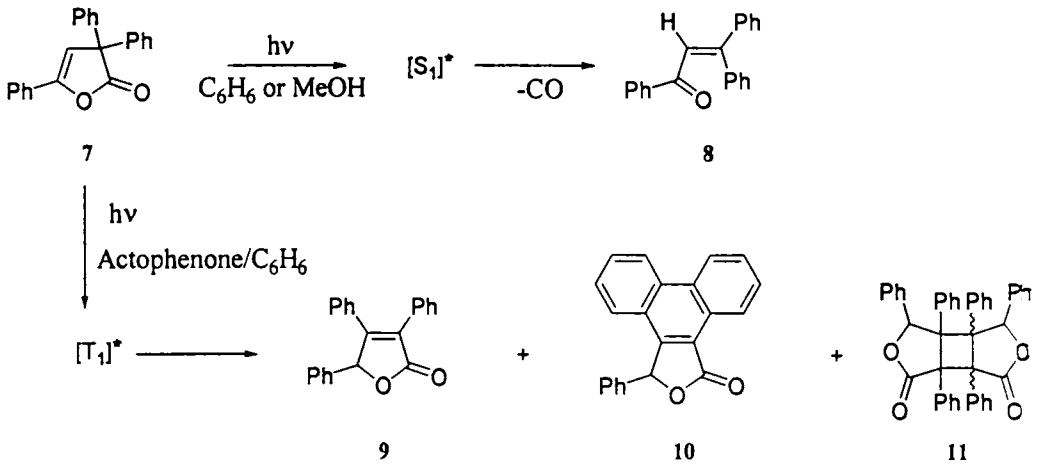
cyclised product, 3-benzyl-3-phenyl-phenanthro[9,10-b]furan-2(3H)-one (**6**) via dihydrophenanthrene intermediate **5** (Scheme 2). The presence of vicinal phenyl groups in the cis configuration at 4- and 5- position of the furananone facilitates the formation of dihydrophenanthrenes.



4 5 6

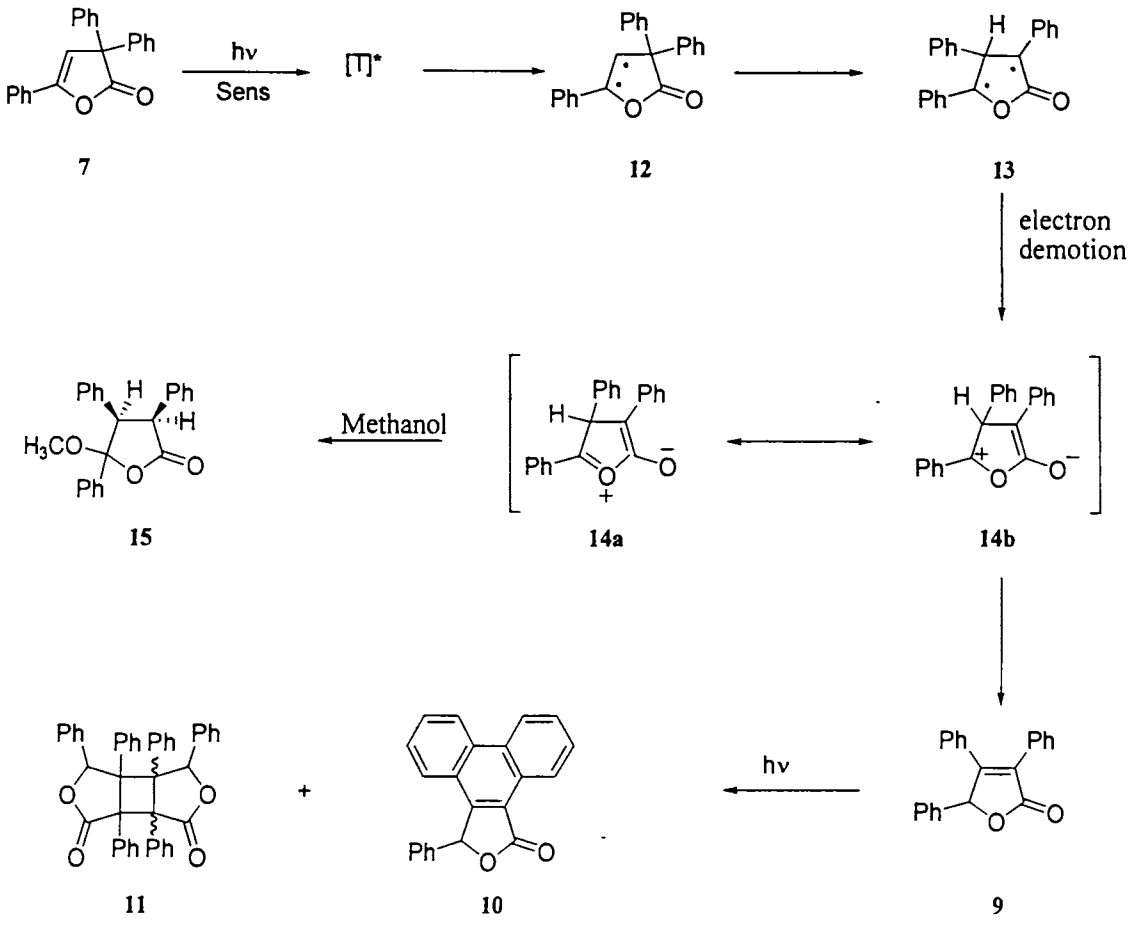
Scheme 2

The prominent excited state reaction pathways available for 3,3,5-triphenyl-2(3H)furanones (**7**) include singlet mediated decarbonylation to give an α,β-unsaturated carbonyl compound **8** and triplet mediated reaction leading to the formation of 3,4,5-triphenyl-2(5H)-furnanone (**9**), and products derived thereof such as 5-phenylphenanthro[9,10-c]furan-2(5H)-one (**10**) and a photodimer tentatively identified as **11** (Scheme 3).[10,11,14]



Scheme 3

The photochemical rearrangement of 3,3,5-triphenyl-2(3H)-furanone to give the corresponding 2(5H)-furanone and the subsequent formation of the phenanthrofuranone can be explained in terms of a pathway involving triplet-excited state.[13] In the triplet-excited state, which can be visualised in terms of a diradical structure, one of the C-3 aryl groups migrates to C-4 to give the rearranged diradical intermediate **13**. Electron demotion in **13** will lead to a zwitterionic intermediate **14**. In the absence of protic solvents, the zwitterionic intermediate undergoes a hydride shift to give the rearranged 3,4,5-triphenyl-2(5H)-furanone (**9**) which in turn absorbs light and undergoes further photocyclisation leading to dihydrophenanthrofuranone (**10**). Alternatively, the 2(5H)-furanone **9** can undergo 2+2 photocycloaddition leading to the dimeric product **11**. Further evidence for the involvement of zwitterionic intermediate **14** is available through trapping experiments.[13] In the presence of methanol, the zwitterionic intermediate is trapped to give the methanol adduct **15** (Scheme 4). Since the physical data available on dimer **11** is scarce, the structural assignment is, at best, tentative. It is equally probable that **7** itself can undergo dimerisation in a head-to-head (HH) or head-to tail (HT) fashion to give the corresponding dimmers. Based on available data, it is not possible to assign the structure of the dimer unequivocally.



Scheme 4

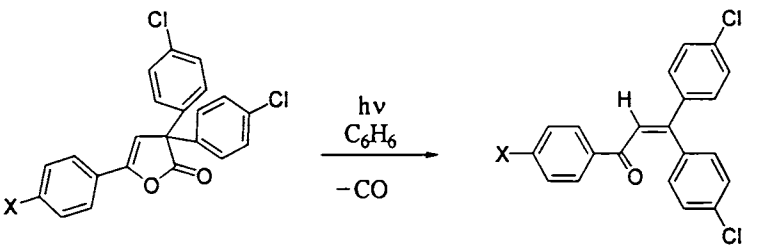
Studies on the effects of substituents at the C-3 position of 3-aryl-3,5-diphenyl-2(3H)-furanones reveal that the triplet decay of these photoreactive 2(3H)-furanones is predominantly controlled by the aryl group migration.[11] The reaction rate is slowed down by both electron-releasing and electron-withdrawing substituents at the 4-position of the phenyl group at the C-5 position of the aryl substituted 2(3H)-furanones.[13]

In the present study we have examined the singlet and triplet mediated photochemical transformations of 5-aryl-3,3-bis(4-chlorophenyl)-2(3H)-furanones with a view to understand the effect of substiutents at the 3 and 5 positions of furanones on their phototransformations. We reasoned that the nature of substituents at the 4-position of the aryl substituents might have a profound effect on the major reaction pathway followed by these systems. Since zwitterionic

intermediates are invoked, development of an electron deficient center at C-5 is conceivable. Hence, the nature of substituents at this position should have a decisive role in controlling the reactivity of these furanones. In this chapter, we describe our findings on the direct as well as sensitized irradiation studies on several 3,3,5-triaryl-2(3H)-furanones.

7.2. Results and Discussion

To study the effect of substituents on aryl groups at the 3- and 5-positions of aryl groups in controlling the nature of photochemical transformations of 3,3,5-triaryl-2(3H)-furanones we synthesised a few 5-aryl- 3,3-bis(4-chlorophenyl)-2(3H)-furanones **16a-d** . The synthesis and characterisation of **16a-d** are discussed in detail in Chapter 2 of this thesis. On irradiation in benzene as well as in acetone, 5-aryl- 3,3-bis(4-chlorophenyl)-2(3H)-furanones **16a-d**, like other 3,3,5-triaryl-2(3H)-furanones, underwent decarbonylation to yield the corresponding α,β-unsaturated product **17a-d** (Scheme 5).



16a-d a) X = H b) X = CH_3 c) X = OCH_3 d) X = Cl **17a-d**

Scheme 5

Compound **17a** was obtained in 44% yield and showed strong absorptions at 1657 and 1600 cm^{-1}. In the ^1H NMR spectrum, the vinylic and aromatic protons were observed as a multiplet at δ 7.2– 7.7. The ^{13}C NMR data showed supportive evidence to the structure. Mass spectrum of the compound revealed the molecular ion peak of this compound at *m/z* 353/355 further confirming its identity. The structure was further confirmed by elemental analysis that gave acceptable data. Based on these spectral data and literature precedences on the photochemistry of

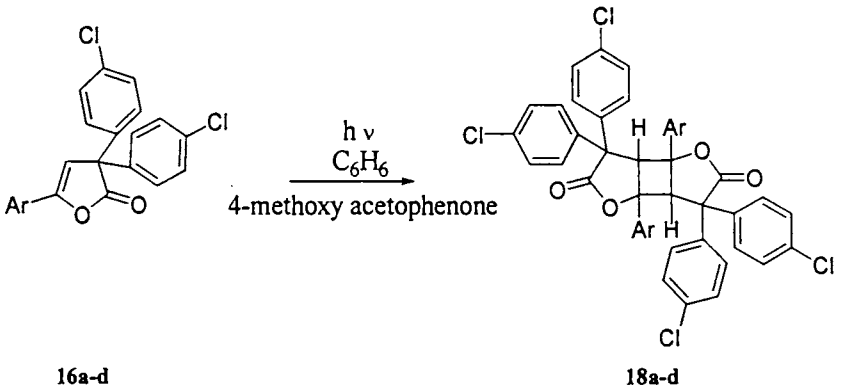
2(3H)-furanones, we identified the photoproduct as α,β-unsaturated compound **17a**.

Compound **17b, 17c** and **17d** showed similar spectral behaviour to those of **17a**. IR spectra showed strong absorptions around ~1657 and ~1603 cm^{-1}. In the ^1H NMR spectrum, the vinylic and aromatic protons were observed as a multiplet around ~δ 7.2– 7.7. Structure of the photoproducts was further confirmed by elemental analysis that gave acceptable data.

Compound **16a-d** on irradiation in benzene in presence of 4-methoxyacetophenone as sensitiser yielded a product that exhibited poor solubility in common organic solvents and melting above 300 ^0C. Earlier reports on aryl substituted 2(3H)-furanones[10,11,14] suggested that these compounds on sensitised irradiation undergo 1,2-phenyl migration leading to 2(5H)-furanones which further undergo 2+2 addition to give corresponding dimer. Based on the physical behaviour of the product obtained by us as stated above and literature precedence, we concluded that the product, indeed, is a dimer. Intriguingly, formation of other products arising through aryl migration such as 2(5H)-furanones and phenanthrofuranones was not detected. These observations could be justified based on two arguments: 1) the 2(5H)-furanone formed underwent fast dimerisation under the conditions employed by us, or 2) the dimer obtained from this reaction may not be arising through the dimerisation of 2(5H)-furanone. Dimerisation of the starting 2(3H)-furanone is, hence, a distinct possibility. In order to establish the identity and origin of the dimer, we explored the concentration dependence on the dimerisation reaction. We reasoned that at low concentration, bimolecular processes like dimerisation should be less probable compared to unimolecular processes such as aryl migration and consequent electrocyclic reactions. Though we examined the photochemistry of 2(3H)-furanones **16a** under different concentrations, unfortunately dimer formation was the only observed transformation.

Since concentration-dependent studies failed to resolve the uncertainty regarding the structure of the dimer, we explored the possibility of assigning the

structure on the basis of spectral data. Though the products exhibited poor solubility in common solvents, we could record ^{1}H NMR and ^{13}C NMR spectra of acceptable quality of a representative sample such as **18b**. ^{1}H NMR spectrum of the dimer **18b** showed a sharp singlet at δ 4.9. In the ^{13}C NMR spectrum, signals attributable to aliphatic carbons were observed at δ 62.8, δ 65.3 and δ 88.5. Out of these, the signal observed at δ 62.8 and δ 65.3 corresponds to a CH whereas the signal at δ 88.5 attribute to the tetrasubstituted carbons. Based on the wide difference in the chemical shift positions of the two tetrasubstituted carbons, we concluded that the signal observed at δ 88.5 is due to a carbon attached to oxygen. If the dimer is arising through the dimerisation of the rearranged 2(5H)-furanone (Figure 2), the methine signal would have appeared more downfield with concomitant shift the peak position of tetrasubstituted carbons. Based on these data we concluded that the structure of the dimer is better represented as **18a-d** arising through the head-to-tail (HT) dimerisation of starting 2(3H)-furanone itself (Scheme 6).



16a-d **18a-d**

a) Ar = C_6H_5 c) Ar = C_6H_4-OCH_3(*p*)
b) Ar=C_6H_4-CH_3(*p*) d) Ar = C_6H_4-Cl(*p*)

Scheme 6

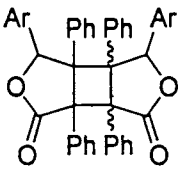


Figure 2

Photoproducts obtained in the sensitised irradiation of **16b,c** and **d** also exhibited similar physical characteristics to those **18a**. Based on this, we conclude that dimersation is the only reaction pathway available to 3,3-bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones. This is in contrast to the facile aryl migration reaction observed with other 3,3,5-triaryl-3H-furan-2-ones reported earlier.[11] Based on available data, the origin of this discrepancy cannot not be identified clearly.

7.3. Conclusion

3,3-Bis(4-chlorophenyl)-5-aryl-3H-furan-2-ones on direct irradiation in benzene and acetone underwent singlet mediated decarbonylation to give α,β-unsaturated carbonyl compounds. On sensitized irradiation they underwent 2+2 cycloaddition to yield the dimer. Based on detailed NMR spectral analysis, we have demonstrated that the structure and origin of the photodimer obtained in the irradiation of 2(3H)-furanones was wrongly represented in literature. We have now assigned the correct structure of the dimer and hence have demonstrated that the dimer is formed by the direct dimerisation of the starting 2(3H)-furanone itself.

7.4. Experimental

7.4.1. General procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for think layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker 300 FT NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported as parts per million (ppm) downfield of tetramethylsilane (TMS). Elemental analysis was performed at Regional

Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow. Irradiations were carried out in a Rayonet Photochemical Reactor (RPR 253.7, 300 or 350 nm). Solvents for steady-state photolysis experiments were purified and distilled before use.

7.4.2. Irradiation of 5-aryl-3,3-bis(4-chlorophenyl)-2(3H)-furanones (16a-d)

7.4.2.1. Irradiation of 16a. A solution of **16a** (0.100 g, 0.263 mmol) in 263 mL benzene purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was charged to a column of silica gel. Elution with a mixture (1:1) of hexane and dichloromethane gave **17a** as a light yellow solid.

Compound 17a. (0.040 g, 44%); mp 94-96 ^{0}C; IR (KBr) 1600 and 1657 cm^{-1}due to (C=O) and (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.8 (m, 14H, vinylic and aromatic protons); MS, *m/z* 353 (M^+), 355 (M^++2) and other peaks. Anal. Calcd for $C_{21}H_{14}Cl_2O$: C, 71.40, H, 3.99. Found: C, 69.71, H, 3.87.

In a repeat run, an acetone solution of **16a** (0.100 g, 0.263 mmol) was irradiated for 4 h at 253 nm under analogous conditions and worked up to give **17a** (0.038 g, 42%).

7.4.2.2. Irradiation of 16b. A solution of **16b** (0.100 g, 0.253 mmol) in 253 mL benzene purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was column chromatographed as in the previous case to give **17b** as a light yellow solid.

Compound 17b. (0.035 g, 38%); mp 110 ^{0}C; IR (KBr) 1657 and 1603 cm^{-1}due to (C=O) and (C=C) respectively; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H, CH_3), δ 7.2-7.8 (m, 13H, vinylic and aromatic protons); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.4 (CH_3), 109.8 (CH), 125.3 (CH), 128.8 (CH), 129.1 (CH), 132.8 (C), 133.2 (C), 137.8 (C), 141.2 (C), 152.8 (C), 193.4 (CO) ; MS, *m/z* 367 (M^+), 369

(M^++2) and other peaks. Anal. Calcd for $C_{22}H_{16}Cl_2O$: C, 71.95, H, 4.39. Found: C, 71.21, H, 4.08.

In a repeat run, an acetone solution of **16b** (0.100 g, 0.253 mmol) was irradiated for 4 h at 253 nm under analogous conditions and worked up to give **17b** (0.038 g, 41%).

7.4.2.3. Irradiation of 16c. A solution of **16c** (0.100 g, 0.243 mmol) in 243 mL benzene purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was column chromatographed to give **17c** as a light yellow solid.

Compound 17c. (0.033 g, 35%); mp 112 ^{0}C; IR (KBr) 1657 and 1602 cm^{-1} due to (C=O) and (C=C) respectively; ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.2-7.8 (m, 13H, vinylic and aromatic), δ 3.8 (s, 3H, OCH_3). Anal. Calcd for $C_{22}H_{16}Cl_2O_2$: C, 68.94, H, 4.21. Found: C, 68.78, H, 4.14.

In a repeat run, an acetone solution of **16c** (0.100 g, 0.243 mmol) was irradiated for 4 h at 243 nm under analogous conditions and worked up to give **17c** (0.035 g, 38%).

7.4.2.4. Irradiation of 16d. A solution of **16d** (0.100 g, 0.240 mmol) in 240 mL benzene purged with nitrogen for 20 min was irradiated (RPR, 300 nm, quartz vessel) for 6 h. The reaction was monitored by TLC. Solvent was removed under vacuum and residue was column chromatographed to give **17d** as a light yellow solid.

Compound 17d. (0.040 g, 43%); mp 97-99 ^{0}C; IR (KBr) 1658 and 1601 cm^{-1} due to (C=O) and (C=C) respectively; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.8 (m, 13H, vinylic and aromatic protons). Anal. Calcd for $C_{21}H_{13}Cl_3O$: C, 65.06, H, 3.38. Found: C, 64.92, H, 3.25.

In a repeat run, an acetone solution of **16d** (0.100 g, 0.240 mmol) was irradiated for 4 h at 253 nm under analogous conditions and worked up to give **17d** (0.037 g, 40%).

7.4.3. 4-Methoxyacetophenone-sensitised Irradiation of 16a-d in Benzene

7.4.3.1. Irradiation of 16a. A solution of **16a** (0.200 g, 0.525 mmol) and 4-methoxyacetophenone (0.079 g, 0.525 mmol) in 525 mL benzene purged with nitrogen for 20 min was irradiated (RPR, 300 nm) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was washed with a mixture (1:1) of hexane and dichloromethane to give **18a** as a white solid.

Compound 18a. (0.120 g, 60%); mp > 315 ^{0}C; IR (KBr) 1773 cm^{-1} due to (C=O) of lactone ring. Anal. Calcd for $C_{44}H_{28}Cl_4O_4$: C, 69.31, H, 3.70. Found: C, 69.22, H, 3.62.

In a repeat run a solution of **16a** (0.100 g, 0.262 mmol) in benzene and 4-methoxyacetophenone (0.039 g, 0.262 mmol) is irradiated under similar conditions to yield **18a** (0.058g, 58%).

7.4.3.2. Irradiation of 16b. A solution of **16b** (0.200 g, 0.506 mmol) and 4-methoxyacetophenone (0.076 g, 0.506 mmol) in benzene (506 mL) purged with nitrogen for 20 min was irradiated (RPR, 300 nm) for 6 h. The progress of the reaction was monitored by TLC. Work up of the photolysate as described earlier yielded **18b** as an amorphous white powder.

Compound 18b. (0.102 g, 51%); mp >315 ^{0}C; IR (KBr) 1755 cm^{-1} (lactone C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.1 (s, 3H, CH_3), 4.9 (s, 2H, aliphatic protons), δ 6.6-7.6 (m, 26H, aromatic protons); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.0 (CH_3), 62.8 (CH), 65.3 (C), 88.5 (C), 124.8 (CH), 125.9 (CH), 127.9 (CH), 127.8 (CH), 128.5 (CH), 129.1 (CH), 129.8 (CH), 132.5 (C), 133 (C), 133.5 (C), 137.5 (C), 175.2 (CO). Anal. Calcd for $C_{46}H_{32}Cl_4O_4$: C, 69.89, H, 4.08. Found: C, 69.72, H, 4.98.

7.4.3.3. Irradiation of 16c. A solution of **16c** (0.200 g, 0.486 mmol) and 4-methoxyacetophenone (0.073 g, 0.486 mmol) in 486 mL benzene and purged with nitrogen for 20 min was irradiated (RPR, 300 nm) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was washed with a mixture (1:1) of hexane and dichloromethane to separate **18c** as a white solid.

Compound 18c. (0.088 g, 44%); mp > 315 ^{0}C; IR (KBr) 1771 cm^{-1} (lactone C=O). Anal. Calcd for $C_{46}H_{32}Cl_4O_4$: C, 67.17, H, 3.92. Found: C, 67.05, H, 3.84.

7.4.3.4. Irradiation of 16d. A solution of **16d** (0.200 g, 0.482 mmol) and 4-methoxyacetophenone (0.072 g, 0.482 mmol) in 482 mL benzene and purged with nitrogen for 20 min was irradiated (RPR, 300 nm, pyrex vessel) for 6 h. The progress of the reaction was monitored by TLC. Solvent was removed under vacuum and residue was worked up as in the earlier cases to separate **18d** as a white solid.

Compound 18d. (0.080 g, 40%); mp > 315 ^{0}C; IR (KBr) 1770 cm^{-1} (lactone C=O). Anal. Calcd for $C_{44}H_{26}Cl_6O_4$: C, 63.56, H, 3.15. Found: C, 63.45, H, 3.06.

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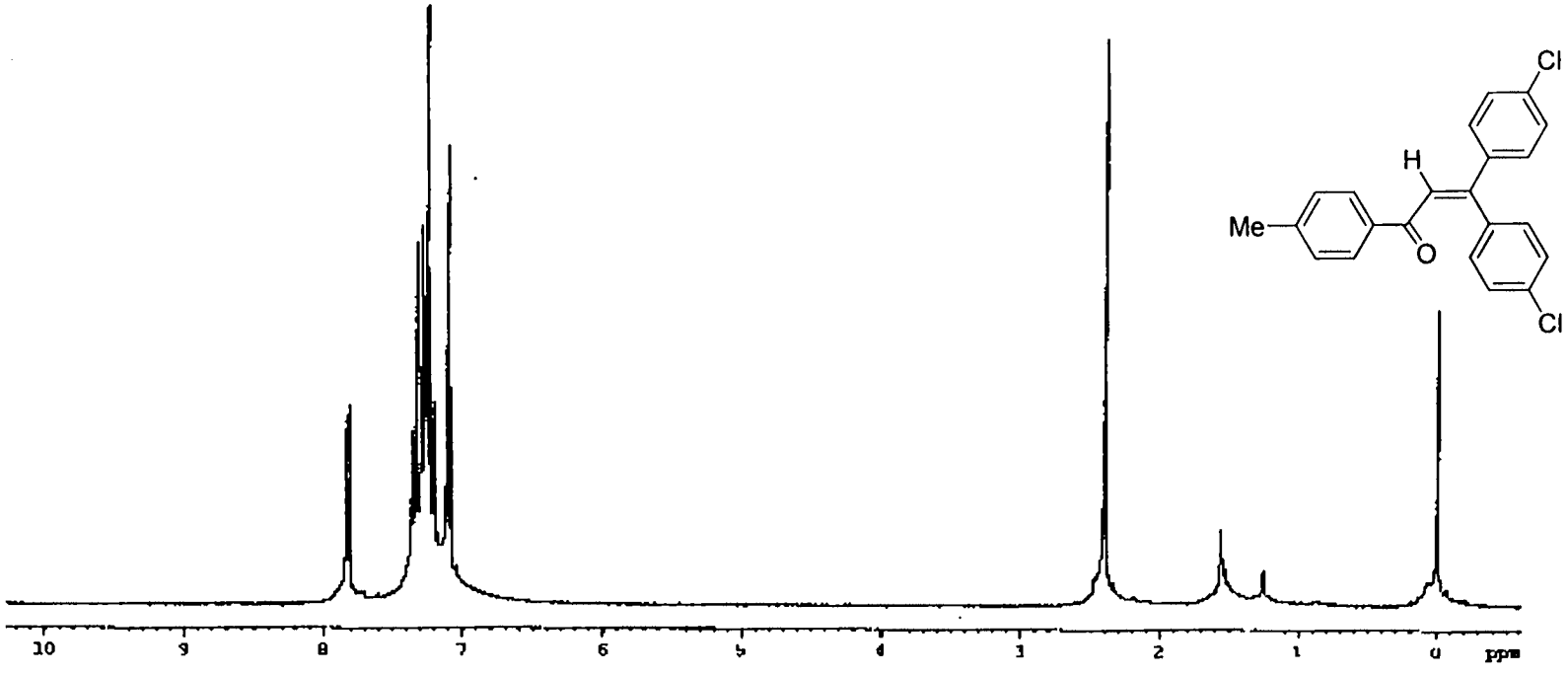


Figure 1. ^{1}H NMR Spectrum of compound 17b

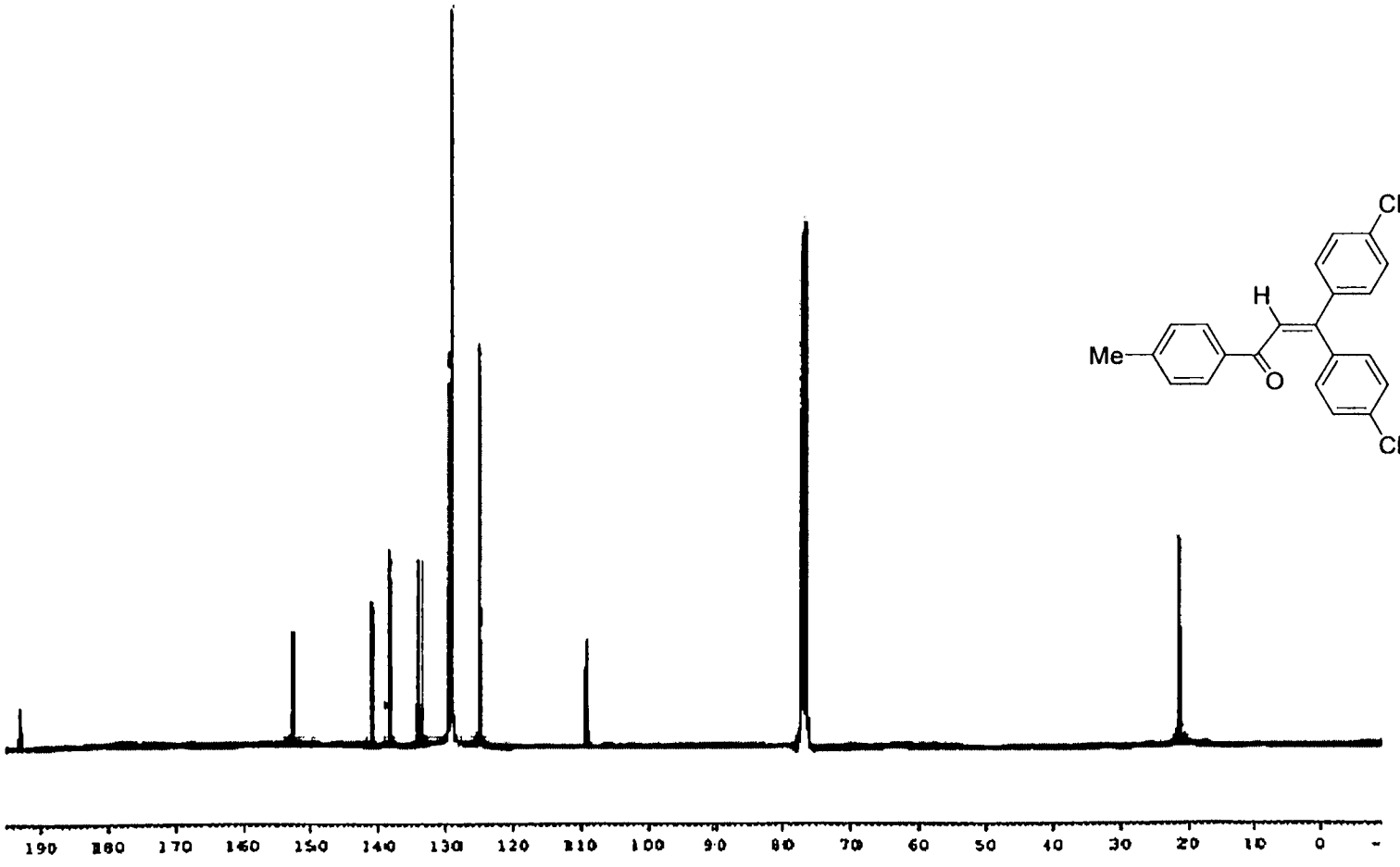


Figure 2. ^{13}C NMR Spectrum of compound 17b

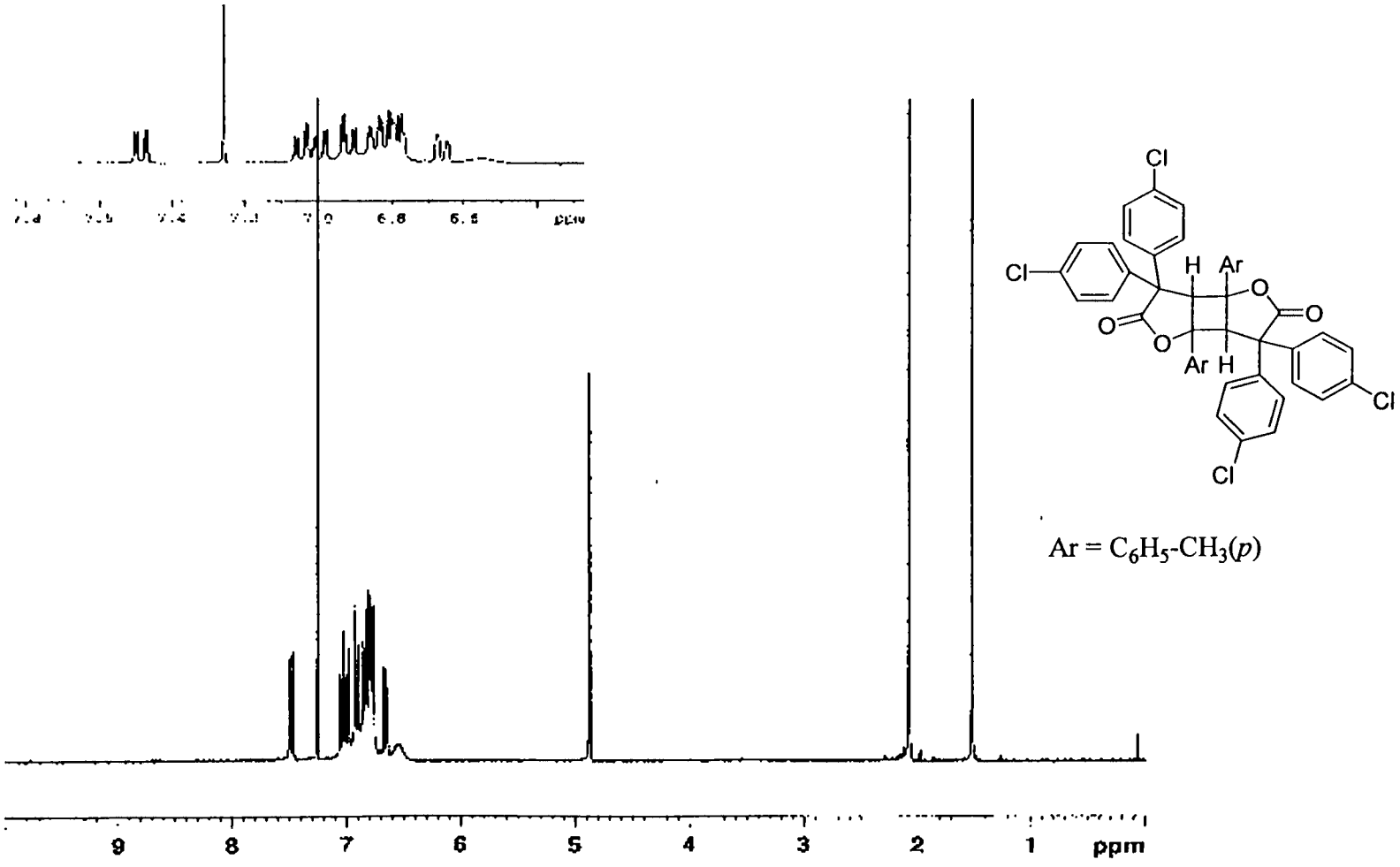


Figure 3. ^{1}H NMR spectrum of compound 18b

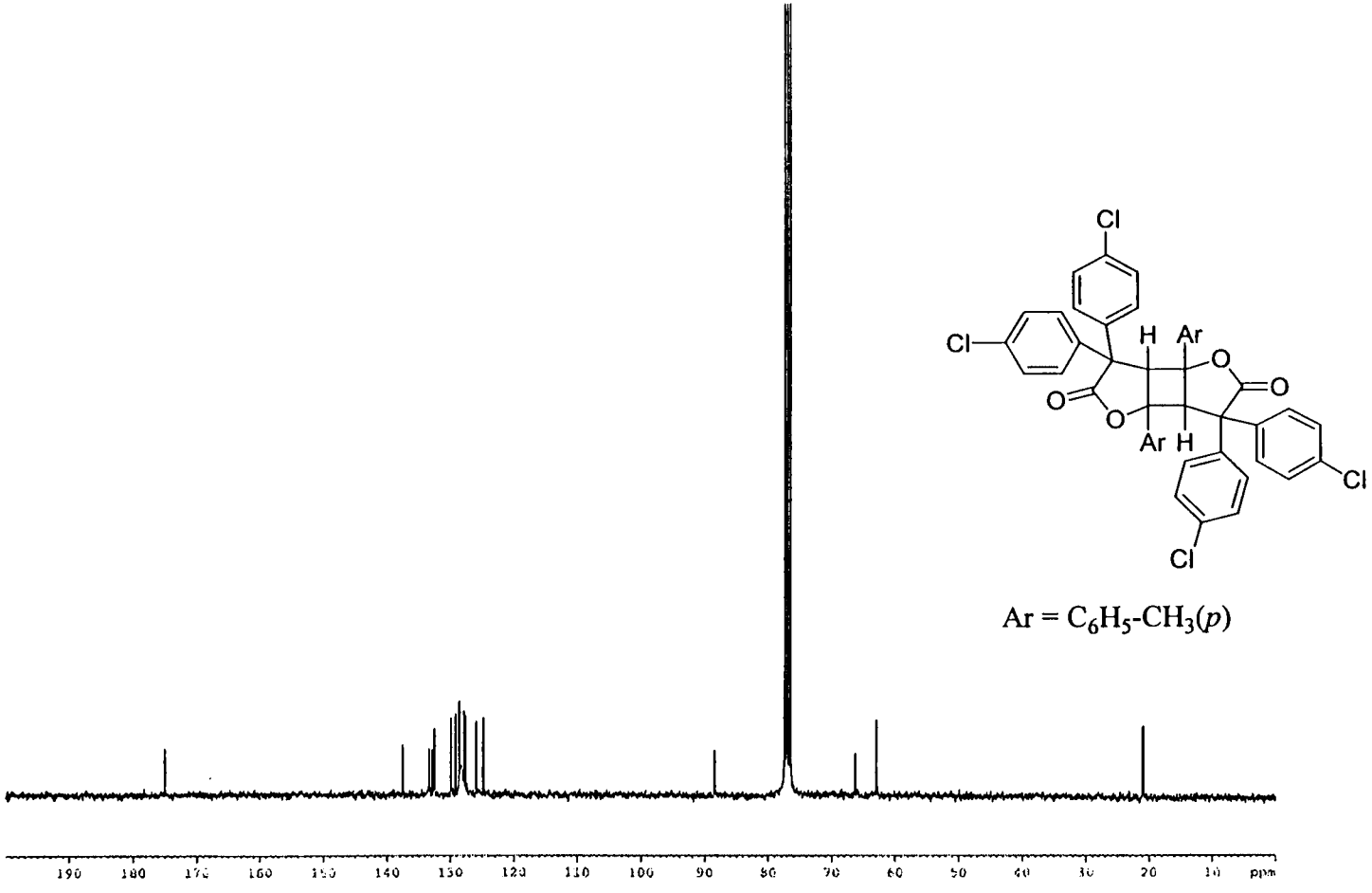


Figure 4. ^{13}C NMR Spectrum of Compound 18b

Chapter 8

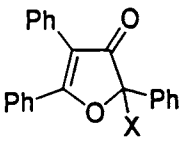
THERMAL AND PHOTOCHEMICAL TRANSFORMATIONS OF 3(2H)-FURANONES

Our findings on the preliminary examination of the thermal and photochemical transformations of several 3,5-triaryl-3(2H)-furanones is described in this chapter. While these compounds exhibited thermal stability, they underwent extensive decomposition to intractable mixtures under the influence of light.

8.1. Introduction

Furanone ring systems constitute the active functionality of many natural products, and many synthetic approaches to these materials have been developed and described.[1,2] Many of these naturally occurring furanones, as well as some of their synthetically produced derivatives, exhibit a broad spectrum of biological activity. Some of them exhibit fungicidal, herbicidal, antibiotic, antitumor and antihelminthic properties.[3-7] Their use as reactive intermediates in organic synthesis has also lent importance to this class of compounds.[8-11] Triaryl 2(3H) and 2(5H)-furanones are known to undergo interesting bond reorganization processes thermally and photochemically.[12-24] A few scattered reports indicate that 3(2H)-furanones also undergo interesting photochemical transformations.[25,26]

As a part of our ongoing interest in the synthesis and transformations of triarylfuranones, and on the basis of the information generated on the thermal and photochemical transformations of a few 2(3H)-furanones, we decided to investigate the thermal and photochemical transformations of triaryl-3(2H)-furanones **1a-c** synthesised by us (Figure 1).



1

a) X = $OCOCH_3$
b) X = OCH_3
c) X = Cl

Figure 1

8.2. Results and Discussion

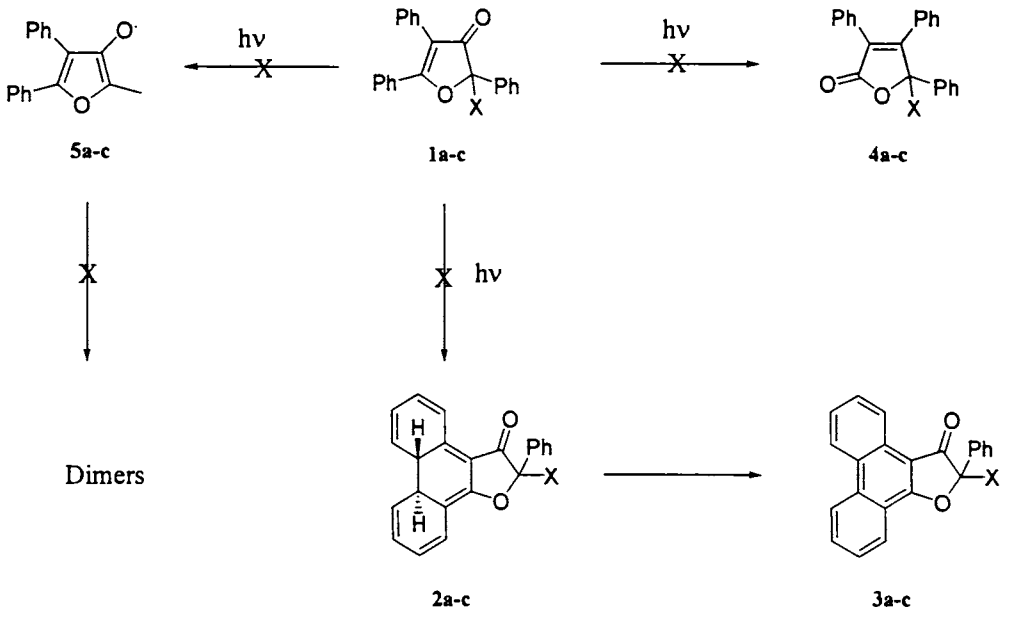
8.2.1. Thermal Transformations

3(2H)-Furanones such as **1a-c** are expected to exhibit useful biological activity.[3-7] The biological activity of these systems may further be fine-tuned by introducing suitable functional groups on the three aryl substituents present in these molecules. Thus, through careful manipulation of the synthetic procedure developed by us,[27]it should be possible to synthesis several 3(2H)-furanones having a myriad of in-built functionalities. A necessary condition for such endeavors is that the parent triphenyl-3(2H)-furanone should exhibit stability towards to a variety of reaction conditions. As a first step, we sought to determine the thermal stability of the parent triphenyl-3(2H)-furanone. To this end, we subjected **1a-c** to heating under a variety of conditions. The conditions employed by us include neat thermolysis in a sealed tube and thermal reaction in presence of a suitable solvent. Under both conditions, the triaryl-3(2H)-furanones were found to be inert.

8.2.2. Photochemical Transformations

Available information on the photochemical transformations of 3(2H)-furanones suggest that they undergo rearrangement to give the corresponding 2(5H)-furanones.[2] Based on this, we expected **1a-c** would also undergo similar rearrangement to give corresponding 2(5H)-furanone, **4a-c**. Additionally, the *cis*-stilbene component present in these molecules may induce competing reaction pathways.[27] This assumption is reasonable since analogous 2(5H)-furanones having *cis*-stilbene components are known to undergo electrocyclic reactions leading to the corresponding phenanthrofuranones as end products. Yet another

possibility is the homolytic cleavage of a suitable functional group leading to furanoxy radical derived dimerisation products.[24] A few of the possible photochemical reaction pathways available to **1a-c** are summarised in Scheme 1.



Scheme 1

Contrary to our expectations, in our hands, 3(2H)-furanones **1a-c** turned out to be highly labile under the influence of light. They underwent extensive decomposition under various irradiations conditions employed by us. No new product could be isolated from any of the reactions carried out by us. In continuation, we examined the photochemistry of **1a-c** in 2-propanol to explore the possibility of photochemical reduction of these molecules. No new products could be isolated from these reactions as well.

8.3. Conclusion

We have established that triphenyl-3(2H)-furanones **1a-c** are relatively stable towards heat. On the other hand, photolysis of these compounds leads to extensive decomposition leading to intractable product mixtures.

8.4. Experimental

8.4.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualisation was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Merck, 60-120 mesh). Infra red spectra were recorded using ABB Bomem FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker 300 FT-NMR spectrometer or a GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. All steady state irradiations were carried out using Rayonet Photochemical Reactor. Solvents for photolysis were purified and distilled before use.

8.4.2. Thermolysis of 3(2H)-Furanones 1a-c

8.4.2.1. Attempted Neat Thermolysis of 1a. A sample of **1a** (0.200 g, 0.54 mmol) was heated in a sealed tube at 225 ^{0}C for 4 h. The product mixture was separated by column chromatography using a mixture (4:1) of hexane and dichloromethane to give unchanged **1a** (0.160 g, 80%).

8.4.2.2. Attempted Neat Thermolysis of 1b. A sample of **1b** (0.200 g, 0.58 mmol) was heated in a sealed tube at 225 ^{0}C for 4 h. The product mixture was separated by column chromatography using a mixture of hexane and dichloromethane (4:1) to give unchanged **1b** (0.150 g, 75%).

8.4.2.3. Attempted Neat Thermolysis of 1c. A sample of **1c** (0.200 g, 0.58 mmol) was heated in a sealed tube at 225 ^{0}C for 4 h. The product mixture was separated by column chromatography using a mixture (4:1) of hexane and dichloromethane to give unchanged **1c** (0.146 g, 73%).

8.4.2.4. Attempted Thermolysis of 1a in Xylene. A sample of **1a** (0.150 g, 0.41 mmol) was taken in xylene (10 mL) and refluxed for 8 h. The progress of the reaction was monitored by TLC. Solvent was removed under reduced pressure and the residue was chromatographed over silica gel. Elution of the column using a mixture (4:1) of hexane and dichloromethane gave unchanged reactant **1a** (0.130 g, 88%).

8.4.2.5. Attempted Thermolysis of 1b in Xylene. A sample of **1b** (0.150 g, 0.44 mmol) was taken in xylene (10 mL) and refluxed for 8 h. Work up of the reaction mixture under conditions analogous to those reported in the previous case yielded unchanged reactant **1b** (0.131 g, 87%).

8.4.2.6. Attempted Thermolysis of 1c in Xylene. A sample of **1c** (0.150 g, 0.43 mmol) was taken in xylene (10 mL) and refluxed for 8 h. Work up of the reaction mixture as in the previous cases yielded unchanged reactant **1c** (0.126 g, 84%).

8.4.3. Photochemcial Transformations of 1a-c

8.4.3.1. Irradiation of 1a.

8.4.3.1.1. In Benzene. A benzene solution of **1a** (0.093 g, 0.25 mmol in 250 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 300 nm, quartz vessel) for 6 h. The progress of the reaction was monitored by TLC. TLC analysis at the end of 6h indicated the formation of multiple products. Solvent was removed under vacuum and the residue subjected to column chromatography over silica gel. No new products could be isolated from this reaction.

1b and **1c** under analogous conditions behaved similar to **1a** resulting in intractable product mixturess.

8.4.3.1.2. In Methanol. A methanol solution of **1a** (0.100 g, 0.27 mmol in 270 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 300 nm, quartz vessel) for 6 h. No new products could be isolated from this reaction also.

Under the same conditions compounds **1b** and **1c** behaved similar to **1a**.

8.4.3.1.3. In Acetone. An acetone solution of **1a** (0.100 g, 0.27 mmol in 270 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 253.7 nm, quartz vessel) for 6 h. Work up of the reaction mixture did not lead to the isolation of any new product.

Compounds **1b** and **1c** also gave multiple products under similar conditions.

8.4.3.1.4. In 2-Propanol. A solution of **1a** (0.100 g, 0.27 mmol) in 2-propanol (270 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 350 nm, quartz vessel) for 6 h. No new products could be isolated from this reaction.

Compounds **1b** and **1c** showed similar behavior under analogous conditions.

8.4.3.1.5. In Benzene-Methanol Mixture. A solution of **1a** (0.100 g, 0.27 mmol in a mixture (1:1) benzene and methanol (270 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 300 nm, quartz vessel) for 6 h. Work up of the reaction mixture did not lead to the isolation of any new product.

Under similar conditions, compounds **1b** and **1c** also yielded multiple products. No new products could be isolated from the reaction mixture.

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Chapter 9

BIOLOGICAL STUDIES OF A FEW 3(2H)-FURANONES

This chapter deals with the studies on the antitumor activity of a few 3(2H)-furanones synthesized by us. *In vivo* and in vitro studies revealed that these 3(2H)-furanones exhibit significant inhibition of tumor cell proliferation.

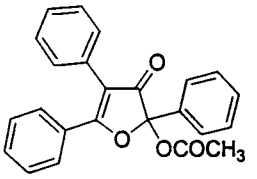
9.1. Introduction

Unsaturated five-membered ring lactones (butenolides) occur widely in nature and possess an unusual range of biological activity.[1,5] They appear throughout the plant kingdom from the simple metabolites of lichens, mold and fungi[6] to the more complex sesquiterpenes of the family Compositae.[7] Moreover, butenolides are observed in such diverse animal species as sponges,[8] butterflies[9] and insects.[10] In the latter species they appear to play a significant role as chemical defense weapons. Butenolides also hold promise as insecticides,[11] herbicides,[12] and seed and plant growth regulators.[13] Of considerable importance is their widespread allergenic,[14] antibacterial,[15] and antifungal[16] activity. Undoubtedly, vitamin C is the most physiologically important butenolide, but tremendous interest has also been generated by the cardiac glycosides, which have the remarkable ability to reduce the frequency, but increase the amplitude of the heartbeat. Several butenolides exhibit cytotoxic and/or tumor inhibitory properties towards a variety of cancers.[17]

5-Methyl-4-hydroxy-3(2H)-furanone is a male pheromone in the cockroach Eurycolis florionda (Walker)[18]. In addition, these compounds can deter grazing by marine herbivores.[19] *It is proposed that the evolved biological function of a number of furanones is to act as inter-organism signal molecules in several different systems. This has resulted in two coincidental effects, which are important for humans. Firstly, the easily oxidisable nature of the furanones in general, which is likely to be an*

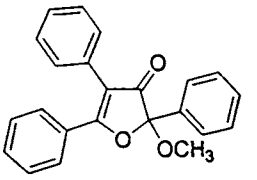
important property in their functioning as signal molecules, results in both mutagenic and anticarcinogenic activity.[20] Furthermore, it is shown that the furanones can interfere with not only intraspecies cell-cell communication, but also interspecies communication in the process of colonization of bacterial communities.[21] Particularly interesting for future research in this area is to assess the potential of amphiphilic furanones that can act in lipid domains within the cell, where ascorbic acid is unable to penetrate.[22]

In an effort to model the biological activity of naturally occurring furanones, we synthesized a few 3(2H)-furanones with hydrophobic groups attached to the furanone ring system and the *in vivo* and *in vitro* antitumor studies of representative compounds (Figure 1) were carried out. The synthesis and characterisation of these compound is discussed in detail in Chapters 4-6. We have limited our investigations on biological activities to one representative example each of the three types of 3(2H)-furanones synthesised by us.



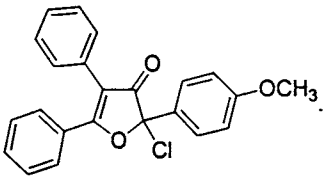
2-Acetoxy-2,4,5-triphenyl-2-H-furan-3-one

1



2-Methoxy-2,4,5-triphenyl-2-H-furan-3-one

2



2-Chloro-2-(4-methoxyphenyl)-4,5-diphenyl-2H-furan-3-one

3

Figure 1

9.2. Results and Discussion

9.2.1. Antitumor Testing Using Animal Model

Oral administration of Compound **1**, **2** and **3** to tumor bearing mice showed significant decrease in the tumor growth (Figure 2). This result clearly suggests that these compounds exhibit very high efficiency in inhibiting tumor cell proliferation *in vivo*.

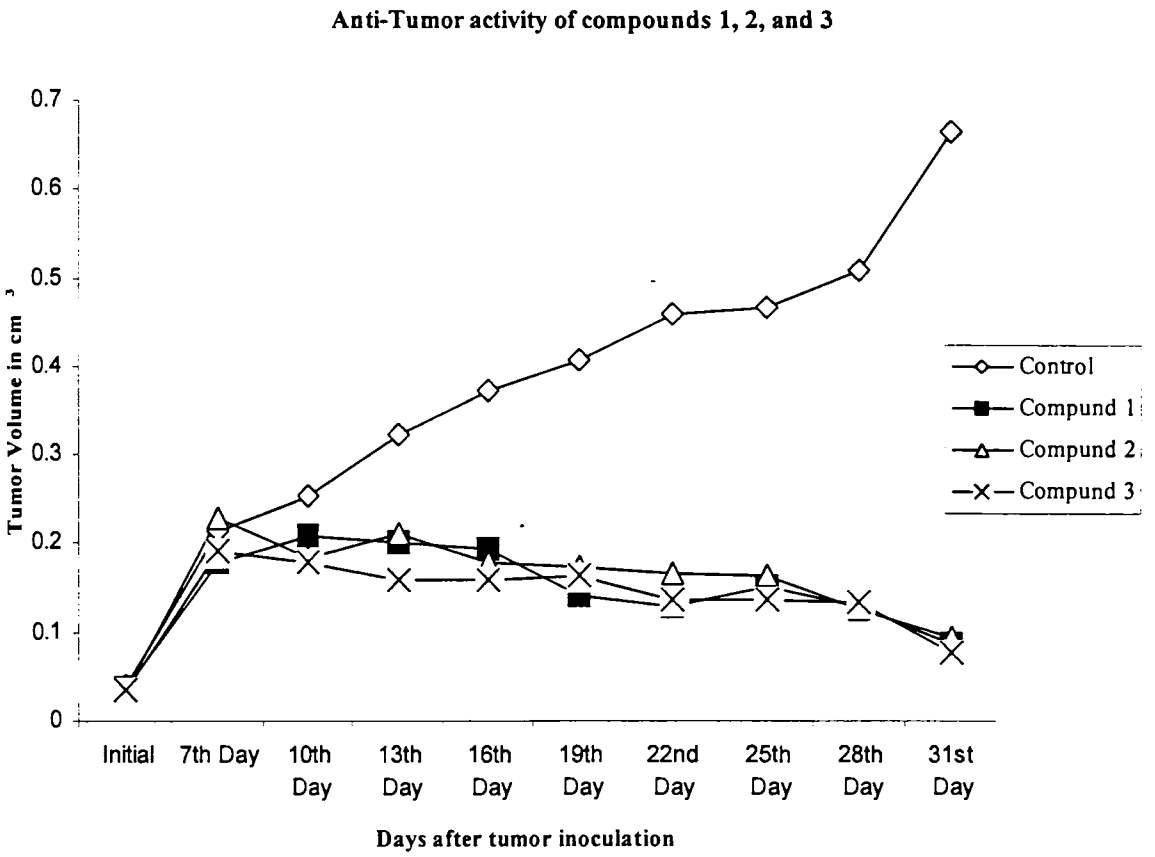


Figure 2

9.2.2. *In vitro* Thymidine Incorporation Assay of 1 and 2

The anti-proliferate effect of the compounds was studied by using DLA cells. The *in vitro* experiments showed that the presence of compounds **1** and **2** could significantly inhibit the proliferation of Daltons Lymphoma Ascits (DLA) cell line *in vitro* (Table, 1) and (Figure 3 and 4). The Effect of various concentrations of compound 1 and 2 on Thymidine incorporation to DNA (DPM/mg protein) of DLA cell line *in vitro* is shown in table 1.

Effect of compound 1 and 2 on DNA synthesis of DLA cell line

Compound	Control	10 µg	20 µg	50 µg	100 µg	200 µg
1	34329 ± 116	23350 ± 201***	22086 ± 463***	20186 ± 267***	19539 ± 212***	17737 ± 252***
2	34329 ± 116	22924 ± 304***	23824 ± 163***	22349 ± 377***	17485 ± 252***	17478 ± 522***

Values are mean ± S.E.M. of 4-6 separate experiments

***$p<0.001$ when compared to control.

Table 1

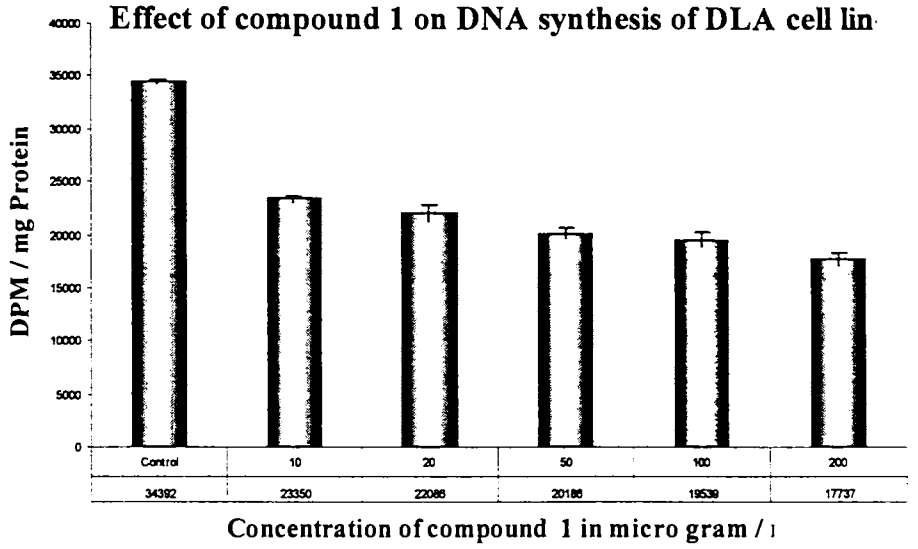


Figure 3

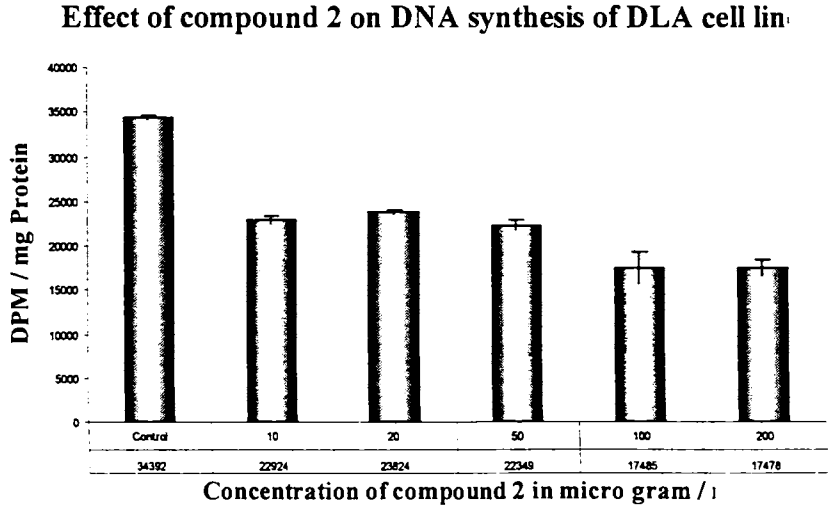


Figure 4

9.3. Conclusion

In vivo and *in vitro* studies of few 3(2H)-furanones synthesised by us showed significiant inhibition of tumor cell proliferation.

9.4. Experimental Procedure

9.4.1. Antitumor Testing Using Animal Model *(In vivo)*

Inbred male Swiss albino mice (6 mice per group) were used to study the *in vivo* antitumor activity of compounds **1**, **2** and **3**. Solid tumor was induced by subcutaneous injection of 1x 10^6 Daltons Lymphoma Ascites (DLA) cells. After seven days of tumor induction, experimental groups received the compounds (1mg per Kg body weight) orally while controls received sterile phosphate buffer saline. Tumor development was measured after each three days using vernier calipers and tumor volume calculated by using formula.

Tumour volume $=4/3\ \pi r_1^2 r_2$ where r_1, r_2 are radius respectively.

9.4.2. Thymidine Incorporation Assay *(In vitro)*

The DLA ($1x10^6$) cells were cultured *in vitro* in the presence of test compounds **1** and **2** concentrations varying from 10 to 200μg. 0.01μCi of Thymidine was added to all the plates. One set was kept as control. After 24 hours of incubation, cells were separated by centrifugation. Cells were digested over night using sodium hydroxide. Radioactivity was measured by using a liquid scintillation counter.

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