Al-Imam Muhammad ibn Saud Islamic University
College of Science
Department of Mathematics

# Synthesis of isoxazolo-1,4-quinones

A graduation research project

submitted to the Department of Chemistry in partial fulfillment of the requirements for the completion of the degree of Bachelor of Science in Chemistry

By

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Under supervision

of

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# Abstract

In the exploration of synthesis and chemistry of isoxazoles, we found that the reaction of aromatic nitrile oxides with the 2-phenyl-[1,4]benzoquinone produced isoxazolo-1,4-[1,4]benzoquinones. This adducts were characterized and their structures were confirmed by nuclear resonance magnetic.

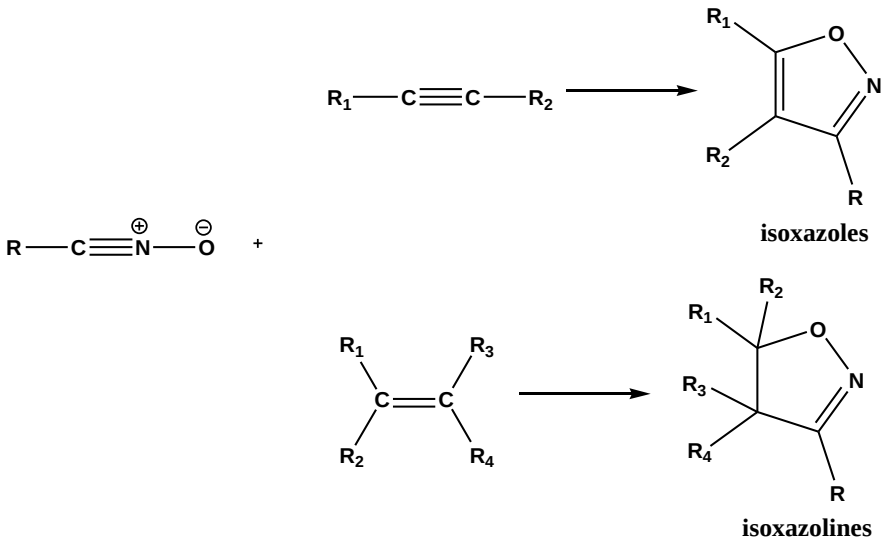
# الخلاصة

قمنا بدراسة تحضير الحلقات الغير متجانسة من نوع الازوكزازول و قد اكتشفنا أن تفاعل أكاسيد النتريل العطرية مع البنزوكينون يعطي حلقات الازوكزازول .تأكدنا من هياكلها بواسطة الرنين النووي المغناطيسي.

# INTRODUCTION

# General Introduction

The addition of a 1,3-dipole to acetylenics and alkenes for the synthesis of five-membered rings is a classic reaction in organic chemistry (1). The 1,3-dipolar cycloaddition reaction of nitrile oxides to acetylenics is an effective procedure for the preparation of isoxazoles (2) (scheme-1), which are intermediates for the synthesis of nitrogen containing a natural product. Based on the literature evidence (3), the isoxazoles formed in the reaction between nitrile oxides and acetylenics are used building blocks; since they are readily converted into 3-hydroxycarbonyl compounds and ß-hydroxyketons.




**Scheme 1 Synthesis of isoxazolines and isoxazoles**

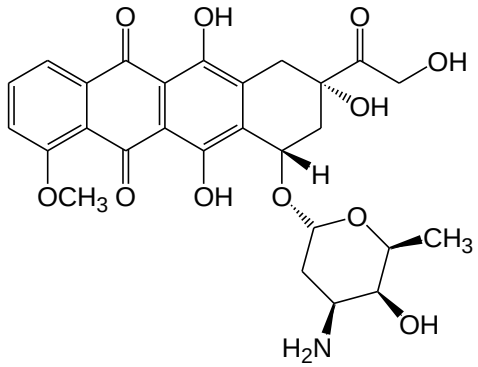
Other useful functional groups, such as 3-aminoalcohols, may also be obtained from isoxazoles. Considerable attention has been given to the synthesis of isoxazoles, both for their high pharmacological and biological activites (4). The role of quinone derivatives in antibacterial and antifungal drugs and growth accelerators for plants has been extensively investigated during the last three decades (5). A number of arylnaphthisoxazolediones was synthesized and investigated in our laboratories (6). Some of isoxazolines show plant-growth regulating activity. In previous papers we have described the development of 1,3-dipolar cycloaddition (7).

In this project we describe the synthesis of a isoxazolo-1,4-quinones. The key step encompasses 1,3-dipolar cycloaddition reactions which are developed in our laboratory (8).

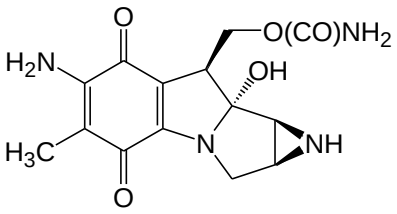
# LITRATURE REVIEW

## 1. Biological activities of some quinone derivatives

The quinone containing compounds have been widely used for their antitumor and anticancer activities. But the problems associated with these compounds such as toxicity and drug resistance have stimulated an intense demand for the discovery of new and novel antitumour agents. In the last few decades significant progress has been made in the screening of quinone containing compounds for antitumour activity. Among a number of cytotoxic antibiotics, a few are clinically tolerable as antitumor agents (9). While antibiotics display an enormous diversity in chemical structures, quinone antibiotics such as adriamycin, mitomycin C, and streptonigrin deserve special attention (Fig. 1).




**adriamycin**




**Mitomycin**

**Figure 1 Quinone antibiotics.**

Although they share a common trait of interference with the synthesis of DNA as well as RNA investigations on their mode of action have revealed an intrinsic characteristic feature of each compound, that is intercalation between stacked base pairs for quinone antibiotics, covalent binding to DNA after the intracellular reduction and superoxide formation through the oxido-reduction cycle. In this context, search of new class of molecules containing quinone moiety has always fascinated the organic as well as medicinal chemist.

Compounds containing the quinone group present an important class of biologically active molecules that are wide spread in nature. Isoxazole derivatives show hypoglemic, analgesic, antiinflammatory, antifungal, anti-bacterial and HIV-inhibitory activities. Synthesis of hybrid natural products has gained momentum in recent years. It is expected that combining features

of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance. There are a few reports describing the preparation of quinone-hybrid with other natural products. For example, quinone-amino acids, sugar-oxasteroidquinone, quinone-annonaceous acetogenins, conduritolcarba-sugar hybrids have been described using different synthetic protocol (10). Quinone-isoxazole hybrid shows significant antifungal activity as well as agricultural application. Arylated quinones possess unique visual and electronic properties that make them useful in photosynthesis and appealing structures to the dye industry. Depending on the substitution pattern, arylated quinones were prepared by a few general methods.

## 2. 1,3-Dipolar Cycloaddition Reactions

The idea of 1,3-dipolar cycloaddition was suggested by Smith in 1938 but this possibility became widely applicable only after 1960, when the reaction was generalized by Huisgen. [4πs+2πs] Cycloaddition is achieved between a dipolarophile (e.g. alkenes, alkynes, carbonyls and nitriles) and a 1,3-dipolar agent (11).

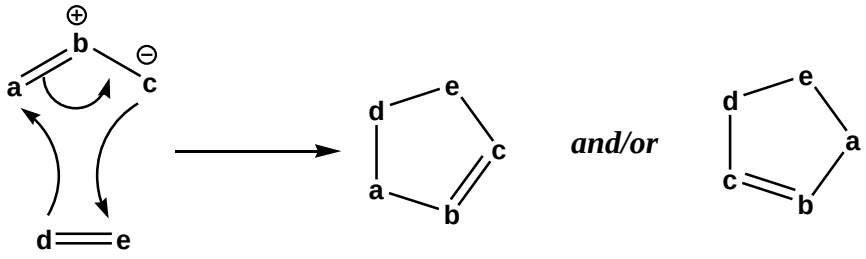



**Figure 2. 1,3-Dipolar cycloaddition reaction**

The 1,3-dipoles form a three-atom π-electron system, with four π-electrons delocalized over the three atoms. Some important 1,3-dipoles are: nitrile oxides, nitrones, azides, nitrile imines, diazoalkanes, carbonyl ylides and nitrile ylides. 1,3-Dipoles can be divided into two types: the allyl type, e.g. nitrones, azomethine ylides, azomethine imines, carbonyl ylides and carbonyl imines, and the propargyl-allenyl type, e.g. nitrile oxides, nitrile imines, nitrile ylides, diazoalkanes and azides. The allyl type contains four electrons in three parallel pz orbitals perpendicular to the plane of the dipole (12). 1,3-Dipoles of the allyl type are bent, whereas a double bond orthogonal to the delocalized π-system in the propargyl-allenyl type confers linearity on the dipole (Figure 3).

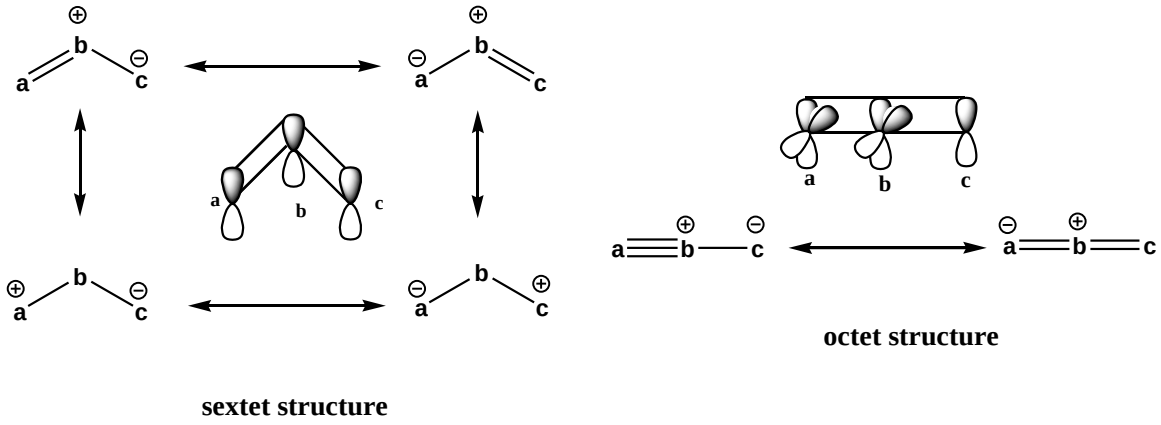
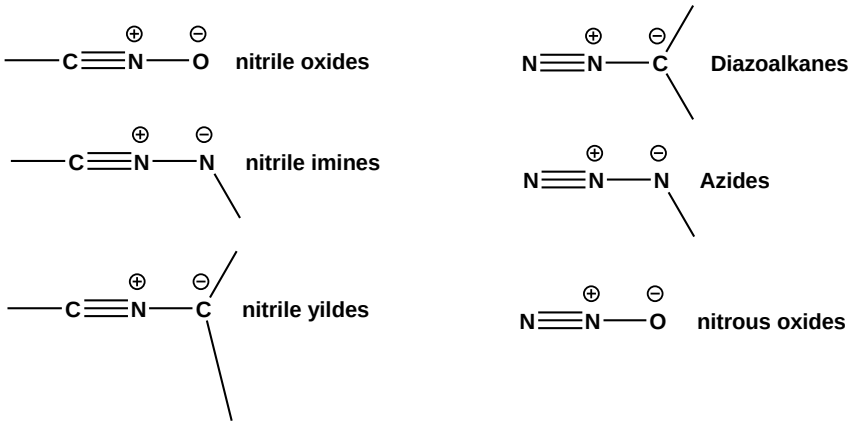


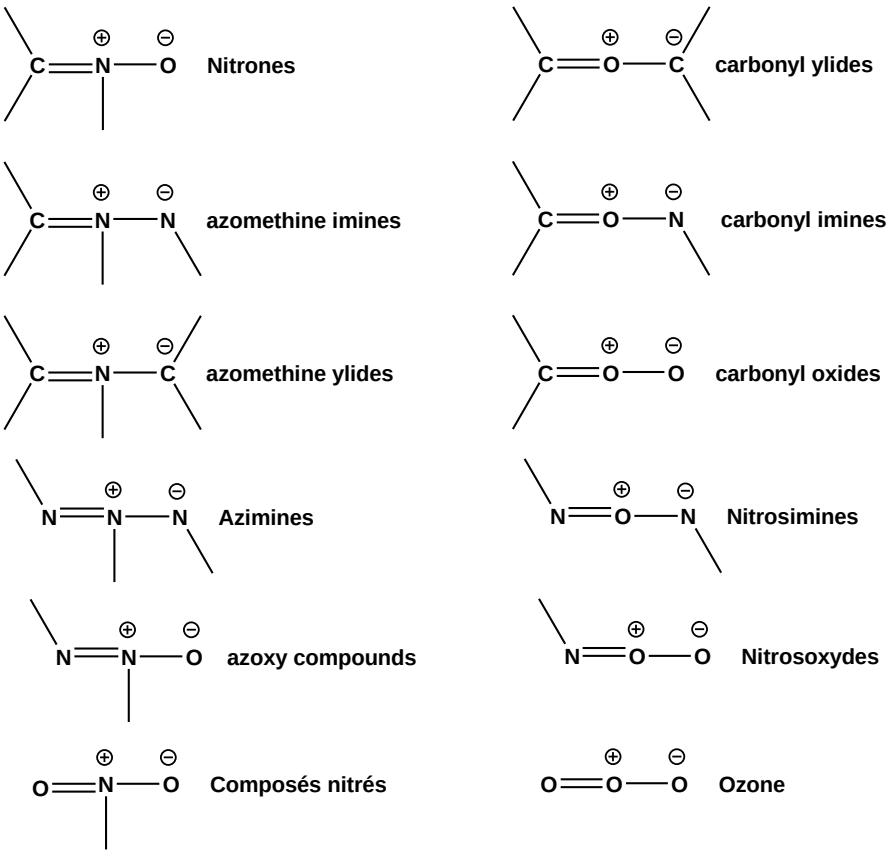

**Figure 3. Octet and sextet structures of 1,3-dipoles.**

*Table 1: Classification of 1,3-dipoles consisting of carbon, nitrogen, and oxygen centers*

**Propargyl-allenyl type**




**allyl type**




### a. Orbital analysis of the 1,3-dipolar cycloaddition reaction

Reactivity in 1,3-dipolar cycloadditions varies considerably and is best explained by the Frontier Molecular Orbital (FMO) model proposed by Fukui, for which he shared the 1981 Nobel Prize [9,10]. In 1,3-dipolar cycloaddition reactions, two new bonds are formed by the use of π electrons of the reactants. In order to form a bond, the highest occupied molecular orbital (HOMO) of one reactant has to overlap with the lowest

unoccupied molecular orbital (LUMO) of the other; in the transition state, stabilization chiefly comes from the overlap in bonding fashion.

### b. The Sustmann classification

According to the Sustmann classification, 1,3-dipolar cycloadditions can be placed in one of three groups with respect to the dominant HOMO-LUMO interaction (13). The classification depends on the number and the nature of the heteroatoms, and on the electron donor/withdrawal properties of any substituents on the reactants (14). This Sustmann grouping indicates whether a high reactivity is expected toward electron-deficient or electron-rich olefins, or to both. The classifications, represented in figure 4, are as follows:

Type I: HOMO (1,3-dipole) – LUMO (dipolarophile) controlled reaction;

Type II: both FMO interactions are of equal importance;

Type III: HOMO (dipolarophile) – LUMO (1,3-dipole) controlled reaction.

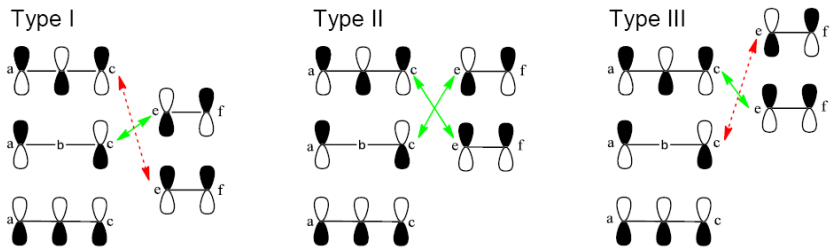



**Figure 4: The HOMO-LUMO interaction between 1,3-dipole a-b-c and dipolarophile (e-f) depends on the orbital energies of the 1,3-dipole: _____ strong and - - - weak interactions.**

**Type I**: This is a HOMO (1,3-dipole) – LUMO (dipolarophile) controlled reaction. The introduction of electron withdrawing groups to ethylene (the parent dipolarophile) lowers both HOMO and LUMO energies (due to a decrease in intra-orbital electronic repulsion) and reduces the energy separation between HOMO (1,3-dipole) and LUMO (dipolarophile) thus accelerating the reaction. Electron donating substituents raise HOMO and LUMO energies in comparison to ethylene (due to an increased intra-orbital

repulsion). This results in an increased energy separation between interacting FMOs which reduces the rate of the reaction. The opposite effect is true for substitution on the 1,3-dipole; acceptor substituents cause deceleration and donor substituents cause acceleration of the rate of the cycloaddition reaction.

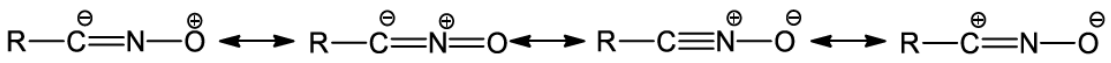
**Type II**: In this case both FMO interactions are of equal importance. Therefore any substituents on the dipolarophile (acceptor or donor) accelerate the reaction rate.

**Type III**: This is a HOMO (dipolarophile) – LUMO (1,3-dipole) controlled reaction. Electron withdrawing substituents on the 1,3-dipole and electron donating substituents on the dipolarophile accelerate these reactions.

## 3. Nitrile Oxide Chemistry

All known methods for the synthesis of nitrile oxides start with organic system already containing -C-N-O sequence of the nitrile oxide structure. Many methods are reported to generate nitrile oxide. The usual synthetic methods of nitrile oxides involve the oxidative dehydrogenation of aldoximes, dehydration of primary nitro compounds and the dehydrohalogenation of hydroxyiminoyl halides. An oxidative dehydrogenation methods of aldoximes to nitrile oxides using oxidants such as lead tetraacetate, alkali hypohalite, *N*-bromosuccinimide in dimethyl formamide followed by base treatment, 1-chlorobenzotriazole are reported. Literature reveals that t-butyl hypoiodite was found to be a powerful reagent for the in situ generation of nitrile oxides under mild conditions.

The resonance forms of these important 1,3-dipoles are shown in scheme 2.



**Scheme 2. Resonance forms of nitrile oxides.**

## 4. Application of Nitrile Oxide Cycloaddition Reactions

1,3-Dipolar cycloaddition of nitrile oxide to different dipolarophiles has been extensively used as a powerful tool in the synthesis of five membered heterocycles.

1,3-dipolar cycloaddition with nitrile oxides is a widely used masked-aldol reaction. Cycloaddition between a nitrile oxide and an alkene yields the cyclic isoxazoline product, whereas the reaction with an alkyne yields the isoxazole (15).

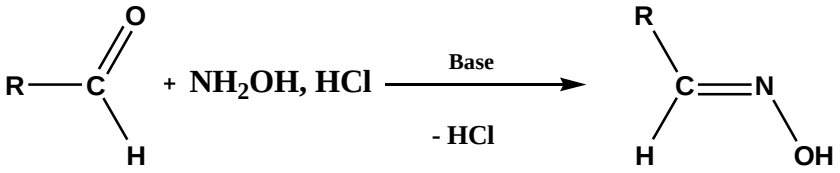
# CHAPTER 2

## 1,3-dipolar cycloadditions of arylnitrile oxides with 2-phenyl-[1,4]benzoquinone

# I. Synthesis of nitrile oxides

## I.1. Synthesis of oximes

Aldehydes reacted smoothly with hydroxylamine hydrochloride in the presence of NaOH to produce high yields of corresponding oximes (16).




**a: R= $C_6H_5$**
**b: R = p-$CH_3OC_6H_4$**

**Scheme 3. Synthesis of oximes**

## I.1. Synthesis of chlorooximes

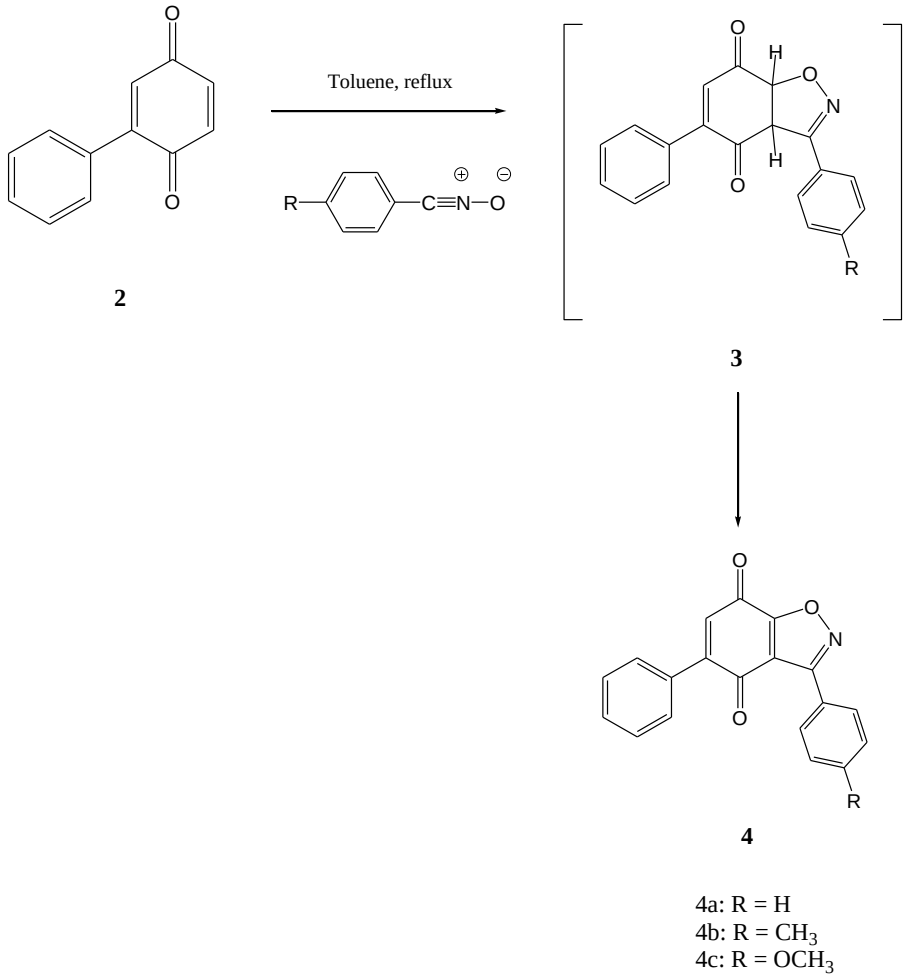
Chlorides hydroxamoyle substituted are prepared by reacting *N*-chlorosuccinimide on the corresponding oxime in anhydrous *N*,*N*-dimethylformamide (Scheme 4) (17).


**a: R= $C_6H_5$**
**b: R= p-$CH_3OC_6H_4$**

**Scheme 4 Synthesis of chlorooximes**

# II. 1,3-dipolar cycloaddition of arylnitrile oxides with 2-Phenyl-[1,4]benzoquinone

The method proposed is relatively very simple, the 1,3-dipolar cycloaddition reaction of *in situ* generated nitrile oxides **1** with 2-phenyl-[1,4]benzoquinones **2** realized in refluxing toluene led to exclusive formation of the isoxazolo-1,4-quinones **4**. In the present case 4 arises by oxidation of initial adduct **3** (Scheme 5), presumably by the action of 1,4-quinones during the reaction, or by atmospheric oxygen during subsequent manipulations; similar behaviours are observed in addition of diphenyldiazomethane to 1,4-naphthoquinone (18).




**Scheme 5 synthesis of isoxazoles**

## III. Structural study of isoxazoles 4

The $^{1}$H-NMR spectra were recorded on a 300 MHz instrument using $CHCl_3$ as the solvent. Structures of a new compound **4a-c** have been elucidated by $^{1}$H-NMR and $^{13}$C-NMR measurements.

$^{1}$H NMR of isoxazole **4c** is recorded in $CHCl_3$. Isoxazole show singlet at 3.88 ppm, which can be attributed to the methoxy group proton. Compound **4c** showed one singlet at 6.95 ppm which can be attributed to the H-7 proton. The aromatic protons are observed at 7.00-8.13 ppm, the four hydrogen atoms attached to the *para*-disubstituted ring gave an AA'BB' spin system (Figure 5).

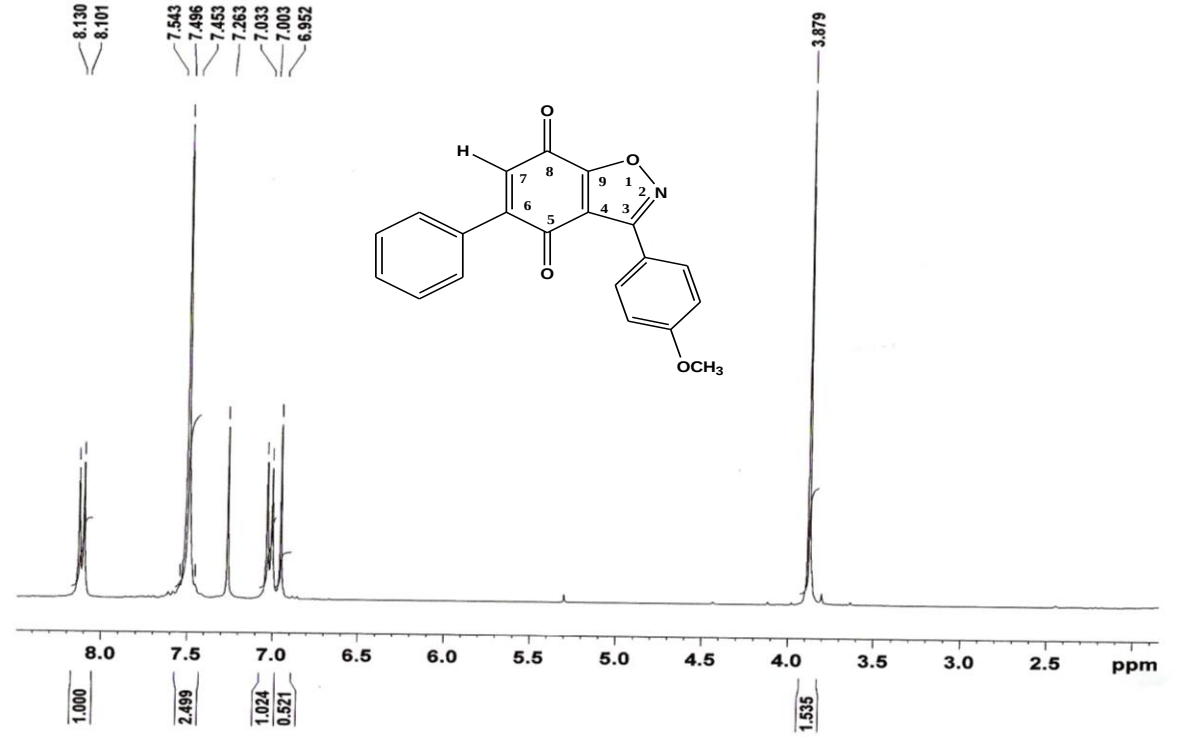



**Figure 5. $^{1}$H-NMR spectrum of isoxazoloe 4c**

The $^{13}$C-NMR spectra of **4c** show a peak at 180.5 and 174.8 ppm, belonging to the two carbonyl carbon (C-5 and C-8). The aromatic carbons are located from 114.2 to 164.9 ppm (figure 6).

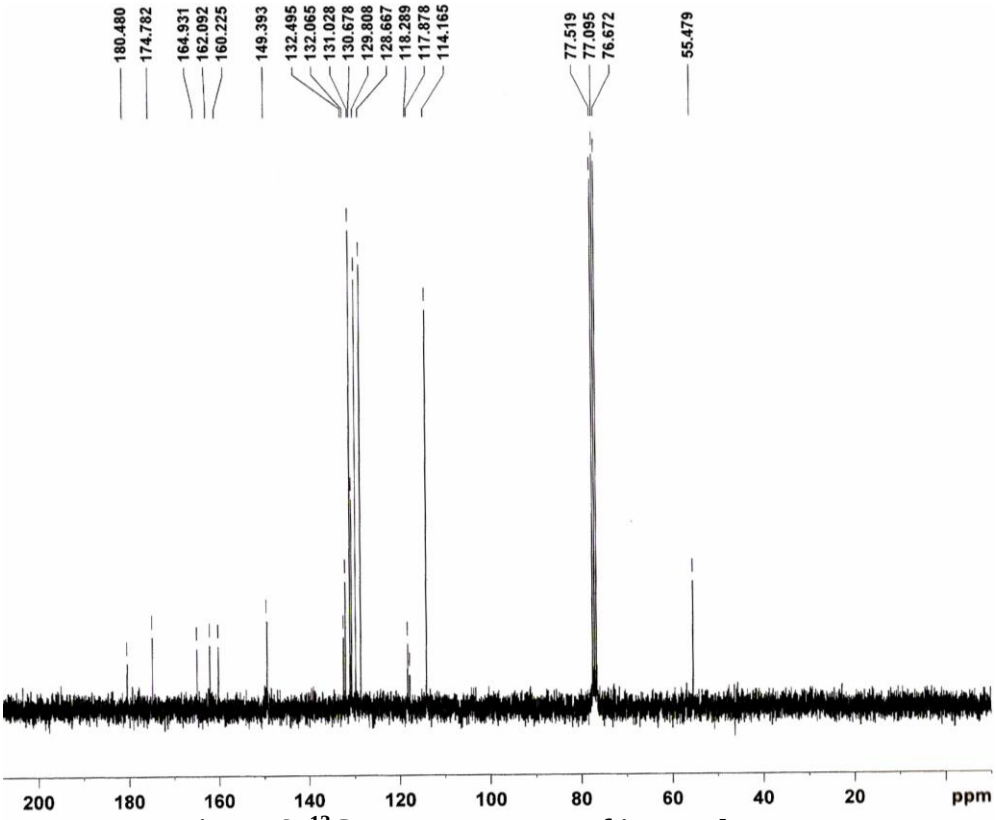



**Figure 6. $^{13}$C-NMR spectrum of isoxazole 4c**

The 1,3-dipolar cycloaddition of nitrile oxides with phenyl-1,4-benzoquinone **2** is, in each case, regiospecific (Figure 7). However, regiochemical an assignment of all adducts were deduced from their $^{13}$C NMR spectra (19).

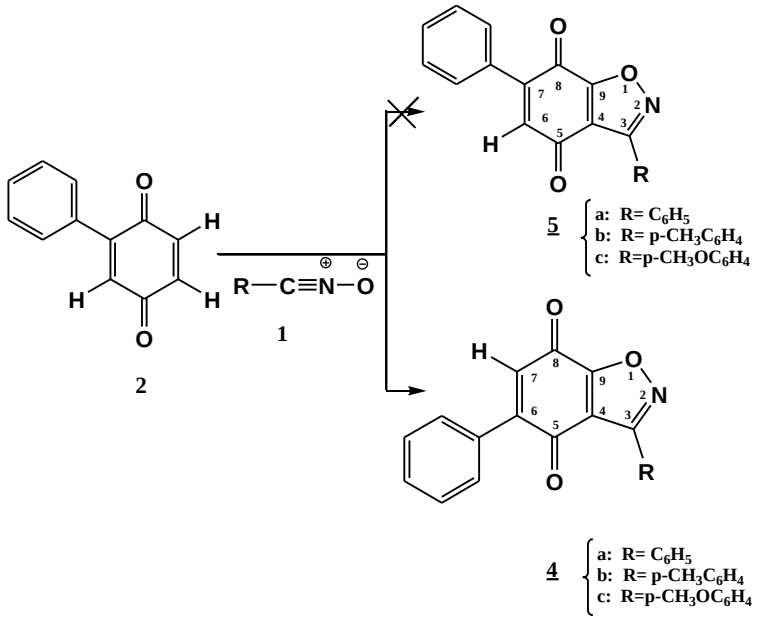



**Figure 7 Regioselectivity of cycloaddition dipolar**

# CHAPTER 3

# Materials and Methods

# 1. Materials

## 1.1. Chemicals

2-Phenyl-[1,4]benzoquinone, hydroxylamine hydrochloride and *N*-chlorosuccinimide were obtained from Sigma Aldrich (St Louis, MO, USA).

# 2. Methods

## 2.1. Proton and carbon NMR Spectrometer

NMR spectra were obtained on a Bruker AC 300 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS) and the coupling constants *J* are given in Hertz. The spectrum was recorded in $CDCl_3$ as solvent at room temperature.

## 2.2. 1,3-dipolar cycloaddition of nitrile oxides with dipolarophile

A solution of dipolarophile 2 (1 mmol) and chloroximes (1.1 mmol) in toluene (10 mL), was stirred at 110 °C. To this solution trimethylamine (0.2 mL), dissolved in toluene (10 mL), was added dropwise. The precipitated triethylammonium chloride was removed by filtration and the filtrate was concentrated in vacuum to afford compounds **4**.

***3,6-Diphenyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4a****:* Brown crystals yield 71%, m.p. 131°C; $^{1}$H NMR ($CDC_{13}$, 300 MHz) δ: 6.91 (s, 1H, H7), 7.39-7.79 (m, 10H, Harom), $^{13}$C NMR ($CDC_{13}$, 75 MHz) δ: 118.42-133.89 (Carom,6,7), 118.31 (C4), 161.88 (C3), 165.30 (C9), 173.29 (C5), 180.52 (C8).

***6-Phenyl-3-tolyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4b****:* Yellow crystals yield 67%, m.p. 152°C; $^{1}$H NMR ($CDC_{13}$, 300 MHz) δ: 2.37 (s, 3H, $CH_3$), 6.90 (s, 1H, H7), 7.26 (d, 2H, Harom) and 7.87 (d, 2H, Harom): AABB' patt. *J* = 7.8 Hz, 7.61 (s, 5H, Harom), 13C NMR (CDC13, 75 MHz) δ: 20.37 (CH3), 116.37-139.61 (Carom,6,7), 118.10 (C4), 160.91 (C3), 164.40 (C9), 173.21 (C5), 179.97 (C8).

***3-Anisyl-6-phenyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4c****:* orange crystals yield 70%, m.p. 163°C; $^{1}$H NMR ($CDC_{13}$, 300 MHz) δ: 3.88 (s, 3H, $OCH_3$), 6.95 (s, 1H, H7), 7.00 (d, 2H, Harom) and 8.10 (d, 2H, Harom): AA BB' patt. *J* = 9 Hz, 7.49 (s, 5H, Harom), $^{13}$C NMR ($CDC_{13}$, 75 MHz) δ: 55.48 ($OCH_3$), 114.16-162.09 ( Carom, 6, 7), 118.29 (C4), 160.22 (C3), 164.93 (C9), 174.78 (C5), 180.48 (C8).

# CONCLUSION

# Conclusion

The reactions of arylnitrile oxides with 2-phenyl-[1,4]benzoquinone have been studied.

1,3-dipolar cycloaddition of arylnitrile oxides with 2-phenyl-[1,4]benzoquinone is taking place regiospecifically.

The isoxazoles **4** arises by oxidation of initial adduct **3**, presumably by the action of 1,4-benzo-quinones during the reaction, or by atmospheric oxygen during subsequent manipulations.

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