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Cycloaddition reaction of *p*-methoxybenzonitrile oxide with 5-hydroxy-1-(4-methoxyphenyl)-3-methyl-1,5-dihydro-2*H*-pyrrol-2-one

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

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Abstract

The reactions of *p*-methoxybenzonitrile oxide with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one has been studied. Nitrile oxide generated *in situ* by addition of triethylamine to (*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride. *p*-methoxybenzonitrile oxide was reacted with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one to give the substituted isoxazole. 1,3-dipolar cycloaddition reaction is taking place regiospecifically. The molecular structure of isoxazoline was determined by ^{1}H NMR and ^{13}C NMR.

الخلاصة

قمنا بهذا المشروع بدراسة التفاعلات القطبية بين مركب نيترايل أكسيد ومشتق الكين. وقد تم تحضير مركب حلقي غير متجانس من نوع الأيزوكزازولين. تم تحديد التركيبة الجزيئية للأيزوكسازولين بواسطة الرنين المغناطيسي النووي.

INTRODUCTION

General Introduction

The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of heterocyclic compounds [1]. It has a nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step. 1,3-dipolar reactions of alkenes with nitrile oxides have been used to prepare isoxazolines. Isoxazolines are a class of heterocyclic compounds having a remarkable number of applications and have been demonstrated to be very versatile building blocks in organic synthesis. The wide range of biological activities includes pharmacological properties such as anti-influenza virus activities [2], antifungal properties [3], anti-inflammatory, antibacterial and HIV-inhibitory activity [4].

The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen-oxygen bond which, under certain reaction conditions, particularly in reductive or basic conditions, is a potential site of ring cleavage The ring opening provides difunctionalized compounds, namely g-amino alcohol, ß-hydroxy ketone, etc., so that isoxazolines can be considered masked forms of these synthetic units [5].

In this line, an impressive effort has been devoted to the synthetic application of the cycloaddition of arylnitrile oxides to alkenes to give isoxazolines.

In this report, we present complete regioselectivity 1,3-dipoar cycloaddition reaction of 5-hydroxy-3-methyl- 1,5-dihydropyrrol-2-one.

In agreement with the aims defined for the present project, the manuscript began with a general introduction, and then a bibliographic revision is made, in chapter 1, concerning the most relevant topics related to the use of 1,3-dipolar cycloaddition.

The second part presents the general methods and the materials utilized in the scope of this project.

The third part contains a general discussion, the major results, and conclusions.

Chapter 1

REVIEW OF LITRATURE

1. 1,3-Dipolar Cycloaddition Reactions

Dipolar cycloaddition reactions fall within the important class of concerted reactions known as pericyclic reactions. In these reactions, all bond breaking and bond making occurs in a single step. The present understanding of the mechanism of pericyclic reactions is mainly due to the work of Woodward and Hoffmann [6]. They recognized that the pathways of such reactions were determined by the symmetry properties of the orbitals that are directly involved, and that the symmetry of each participating orbital must be conserved during the concerted process. The cycloaddition reaction is a process in which two or more π systems combine to form a stable cyclic molecule, during which sigma bonds are formed between the termini of π systems, and no fragment is lost. Two important cycloaddition reactions are the Diels-Alder reaction and the 1,3-dipolar cycloaddition reaction. The general concept of the 1,3-dipolar cycloaddition reaction evolved out of the monumental work carried out by Huisgen and his co-workers in the early 1960's [7]. In this reaction, a five membered ring is formed by the cycloaddition of a three atom entity, (a-b-c), the 1,3-dipole, and a two atom entity, (d-e), the dipolarophile. The reaction can be represented as shown in figure 1. It is a [3+2] cycloaddition reaction and in terms of orbital symmetry, it is classified as [π 4s + π 2s] cycloaddition analogous to the Diels-Alder reaction.

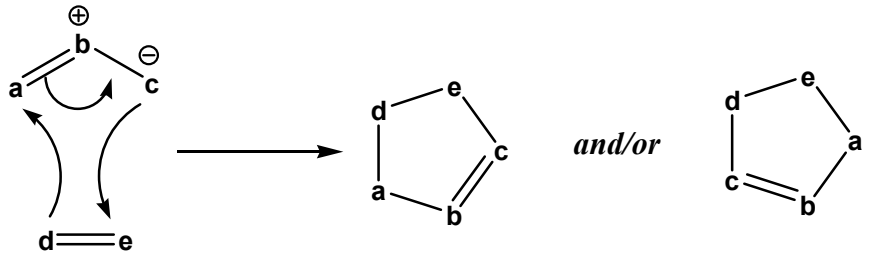


Figure 1. 1,3-Dipolar cycloaddition reaction

1,3-Dipoles molecules can be represented by zwitterionic octet or sextet structures as shown in figure 2. Most commonly, they include a combination of C, O and N atoms. 1,3-Dipoles containing S and P are also found.

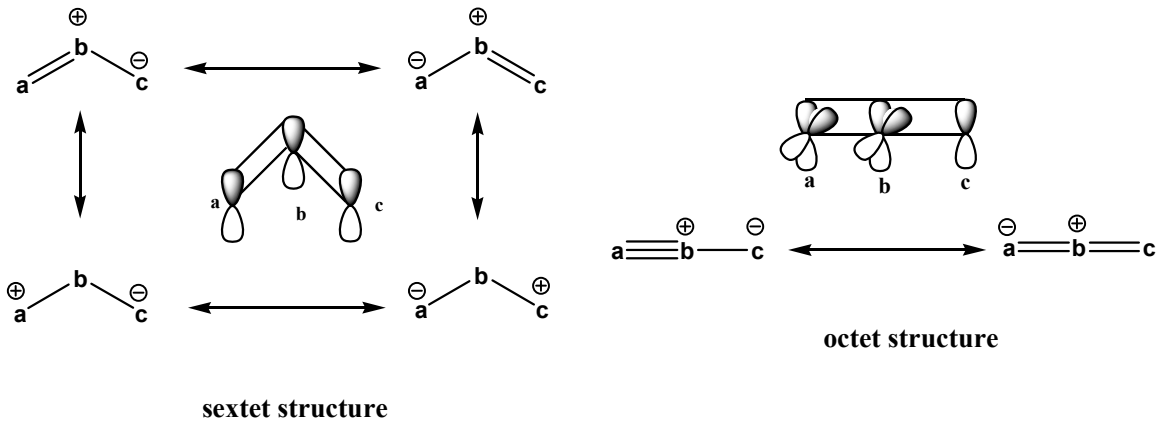
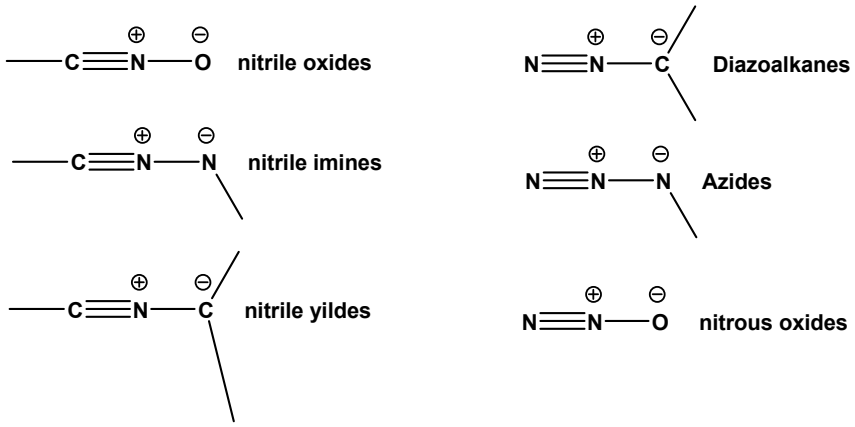


Figure 2. Octet and sextet structures of 1,3-dipoles.

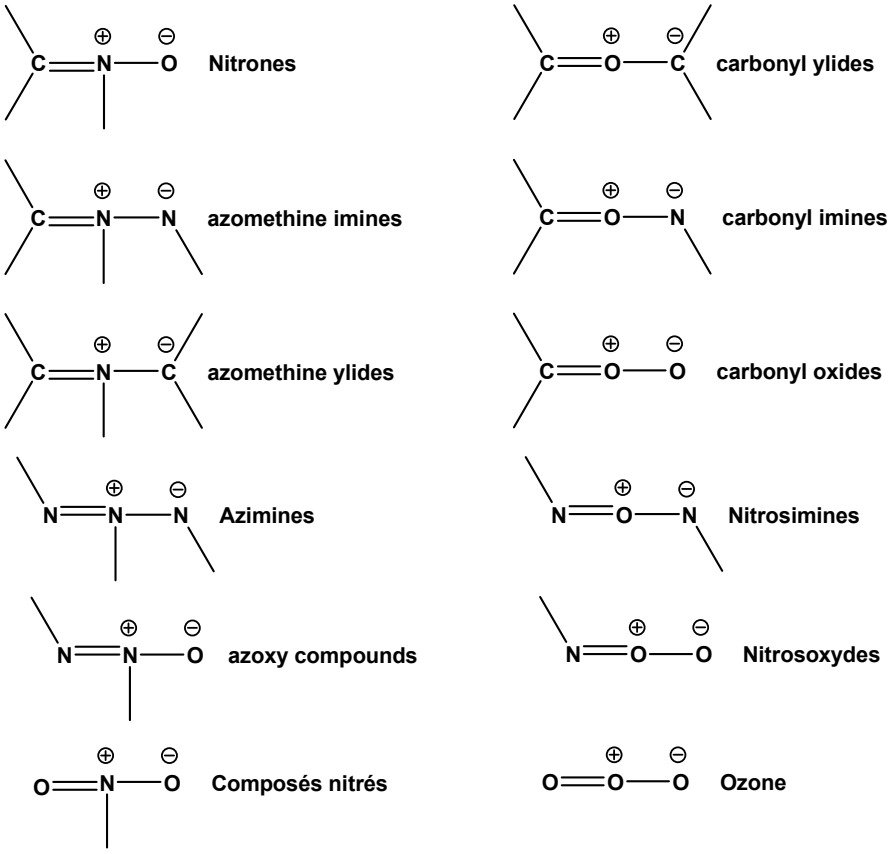
In all 1,3-dipoles (Table 1), there are four electrons in three parallel π orbitals. From the resonance structures contributing to the dipole, it is clear that 1,3- dipoles can be both nucleophilic and electrophilic in nature and this ambivalence is of key importance in understanding their reactivity. For any given dipole, the nucleophilic character may be stronger or weaker than its electrophilic quality, for example, nitrile ylides or diazomethane will cycloadd to electron deficient dipolarophiles much faster than to electron rich multiple bonds. The opposite is true for ozone, which combines preferably with electron rich dipolarophiles [8]. The dipolarophile can be virtually any C=C double or C≡C triple bonded species. Other multiple bonded functional groups such as imines, azo and nitroso moieties can also act as a dipolarophiles. Because of the wide range of structures that can serve either as dipole or dipolarophile, 1,3-dipolar cycloaddition reactions are very useful for the construction of a wide range of five membered heterocyclic rings.

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

Propargyl-allenyl type



allyl type



1.1. 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.

1.2. 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 [11]. 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 [12]. 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 3, 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.

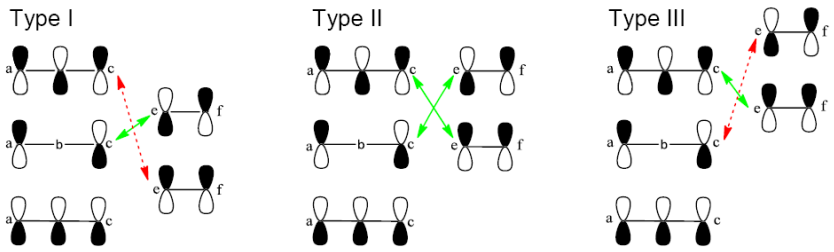


Figure 3: The HOMO-LUMO interaction between 1,3-dipole a-b-c and dipolarophile (e-f) depends on the orbital energies of the 1,3-dipole: _____ strong and - - - weak interactions.

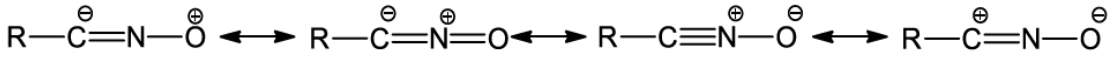
Type I: This is a HOMO (1,3-dipole) – LUMO (dipolarophile) controlled reaction. The introduction of electron withdrawing groups to ethylene (the parent dipolarophile) lowers both HOMO and LUMO energies (due to a decrease in intra-orbital electronic repulsion) and reduces the energy separation between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

2. Nitrile Oxide Chemistry

The parent nitrile oxide, the fulminic acid (HNCO) was discovered in 1800 [13]. One of its most valuable derivatives, benzonitrile oxide, was generated in 1886 by Gabriel and Koppe [14]. The resonance forms of these important 1,3-dipoles are shown in scheme 1.

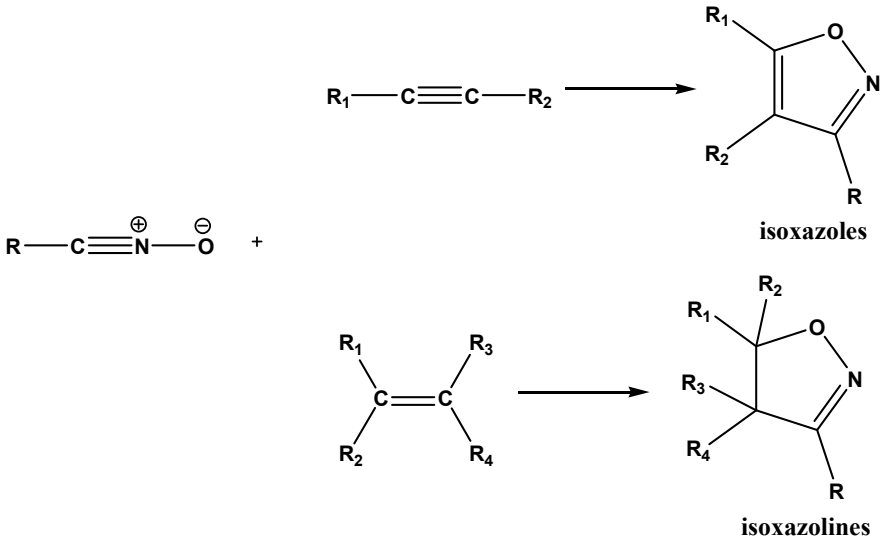


Scheme 1. Resonance forms of nitrile oxides.

2.1. 1,3-dipolar cycloaddition

Alkenes and alkynes serve as excellent dipolarophiles and the ability of nitrile oxides to react with olefins was first recorded by Weygand in l927 [15]. In 1961, Huisgen categorized the nitrile oxide as a member of a broader class of 1,3-dipoles that were

capable of undergoing [3+2]-cycloaddition reactions. Cycloaddition of nitrile oxides to olefins yield isoxazolines while addition to alkynes gives isoxazoles (Scheme 2).



Scheme 2: Cycloaddition of nitrile oxides to olefins and alkynes.

CHAPTER 2

1. Materials

1.1. Chemicals

5-hydroxy-1-(4-methoxyphenyl)-3-methyl-1,5-dihydro-2H-pyrrol-2-one, hydroxylamine hydrochloride, sodium hydroxide and *N*-chlorosuccinimide, dichloromethane were obtained from Sigma Aldrich (St Louis, MO, USA).

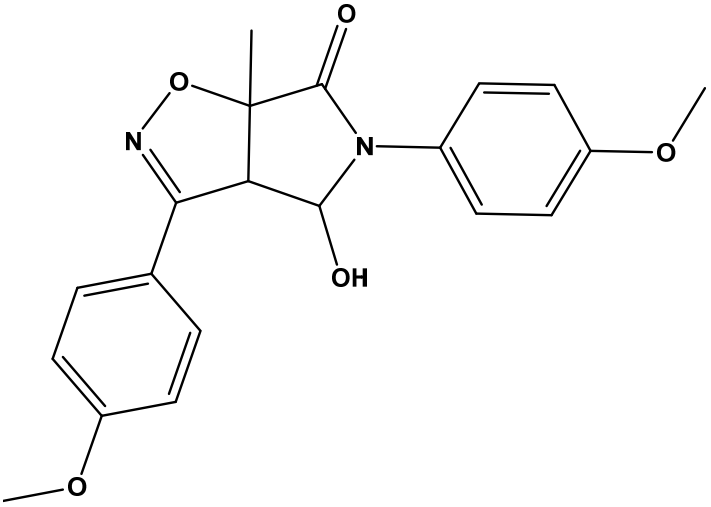
1.2. Proton and carbon NMR Spectrometer

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

2. 1,3-dipolar cycloaddition of p-methoxybenzonitrile oxide with dipolarophile

A solution of dipolarophile 2 (1 mmol) and chloroxime (1.1 mmol) in toluene (10 mL), was stirred at 30 °C. To this solution trimethylamine (0.2 mL), dissolved in dichloromethane (10 mL), was added dropwise. The precipitated triethylammonium chloride was removed by filtration and the filtrate was concentrated in vacuo, and chromatography (SiO_2; ethyl acetate/petroleum ether, 2:1) to afford compound **4**.

4-hydroxy-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-d]isoxazole-6-one (4)



colorless solid. M.p = 222 °C, ^{1}H-NMR (300 MHz, DMSO) d: 1.53 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.56 (s, 1H, OH), 5.41 (d, 1H, 3a-H, J = 9.6 Hz), 6.36 (d, 1H, 4-

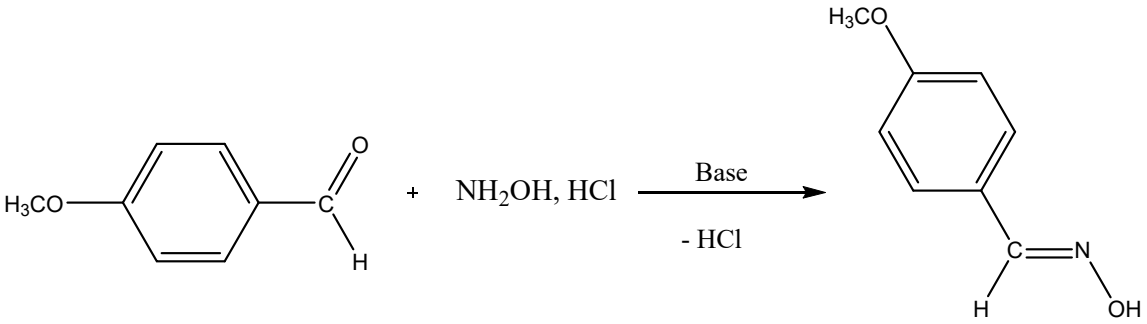
H, J = 9.6 Hz), 6.93 (d, 2H) and 7.02 (d, 2H): AA'BB' part. *J* = 9 Hz, 7.30 (d, 2H) and 7.86 (d, 2H): AA'BB' part. *J* = 9 Hz; ^{13}C-NMR (75 MHz, DMSO) d: 21.6 (CH_3), 55.6 (OCH_3), 55.7 (OCH3), 60.3 (C-3a), 87.9 (C-4), 88.6 (C-6a), 114.1–161.1 (Carom),154.1 (C3), 166.6 (C-6).

CHAPTER 3

I. Synthesis of *N*-hydroxy-4-methoxybenzimidoyl chloride

I.1. Synthesis of oxime 1

4-Methoxybenzaldehyde reacted smoothly with hydroxylamine hydrochloride in the presence of NaOH to produce high yields of corresponding oxime **1** [16].

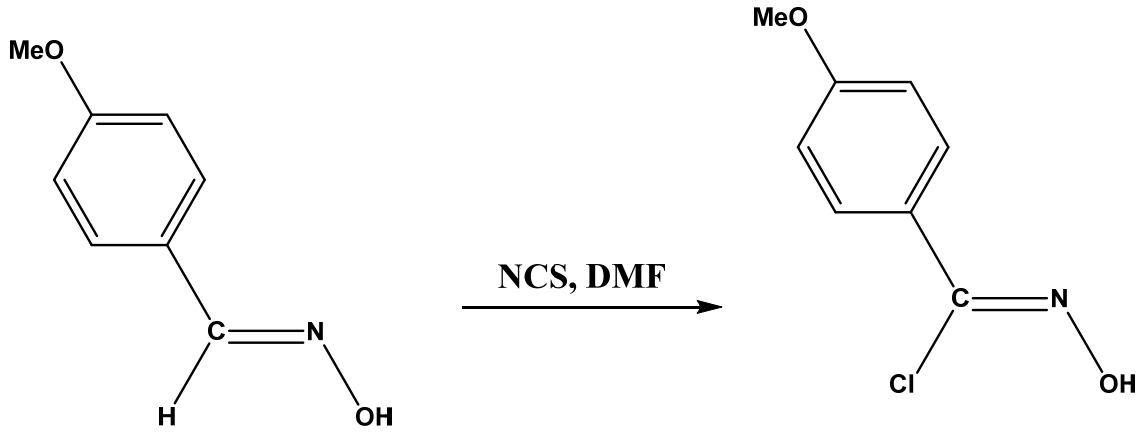


1

Scheme 3: Synthesis of (*E*)-4-methoxybenzaldehyde oxime 1

II.1. Synthesis of *(Z)-N*-hydroxy-4-methoxybenzimidoyl chloride 2

(*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride **2** was prepared by reacting *N*-chlorosuccinimide on the corresponding oxime **1** in anhydrous *N,N*-dimethylformamide (Scheme 4) [17].

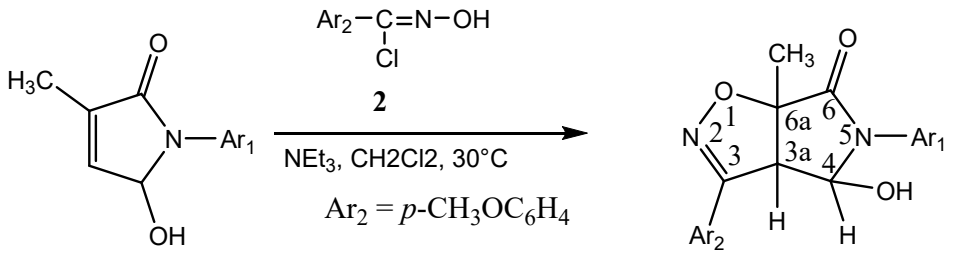


2

Scheme 4: (*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride 2

II. 1,3-dipolar cycloaddition of *p*-methoxybenzonitrile oxide with 5-hydroxy-1-(4-methoxyphenyl)-3-methyl-1,5-dihydro-2H-pyrrol-2-one

The labile *p*-methoxybenzonitrile oxide generated *in-situ* from (*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride **2** was allowed to react with 5-hydroxy-1-(4-methoxyphenyl)-3-methyl-1,5-dihydro-2H-pyrrol-2-one **3** in dichlorometrhane. The reaction proceeded with the formation of one cycloadduct **4** [18].



3

$Ar_1 = p\text{-}CH_3OC_6H_5$

4

$Ar_1 = p\text{-}CH_3OC_6H_5$
$Ar_2 = p\text{-}CH_3OC_6H_5$

Scheme 5: 1,3-dipolar cycloaddition of *p*-methoxybenzonitrile oxide with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one.

We now must determine the addition mode of *p*-methoxybenzonitrile oxide with dipolarophile **3**. Unambiguous proofs for the obtained cycloadducts Regio-chemistry raised from their spectral data. However, regiochemical assignments of adduct 4 was deduced from their 13C-NMR spectra. In particular, the chemical shifts of C-6a are in excellent agreement with those usually obtained when this quaternary carbon is attached to oxygen atom (Figure 4) [19].

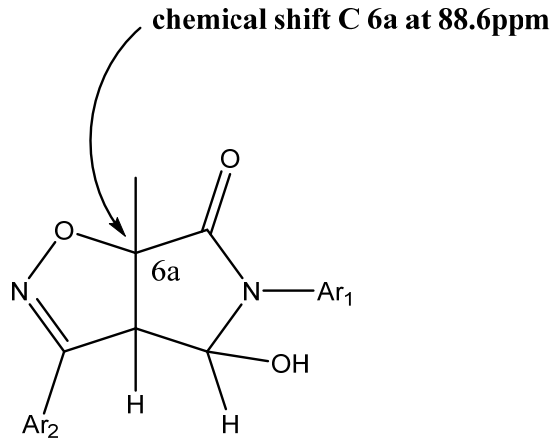


Figure 4: Regiochemistry of cycloadduct

III. Structural study of isoxazoline 4

The ^{1}H-NMR spectra were recorded on a 300 MHz instrument using DMSO-d6 as the solvent. Structure of compound **4** has been elucidated by ^{1}H-NMR and ^{13}C-NMR measurements.

^{1}H NMR of isoxazoline **4** is recorded in DMSO. Isoxazoline show singlet at 2.37 ppm, which can be attributed to the methylene proton. Compound **4** showed two singlets at 3.75 and 3.81 ppm which can be attributed to the methoxy group proton of phenyl ring. The aromatic protons are observed at 6.93-7.83 ppm, the eight hydrogen atoms attached to the *para*-disubstituted ring gave an AA'BB' spin system. Compound **4** showed two peaks as doublets at 5.41 ppm (H_{3a}) and 6.36 ppm (H_4), these confirmed the The *syn* stereochemistry of the 2-isoxazoline (Figure 5).

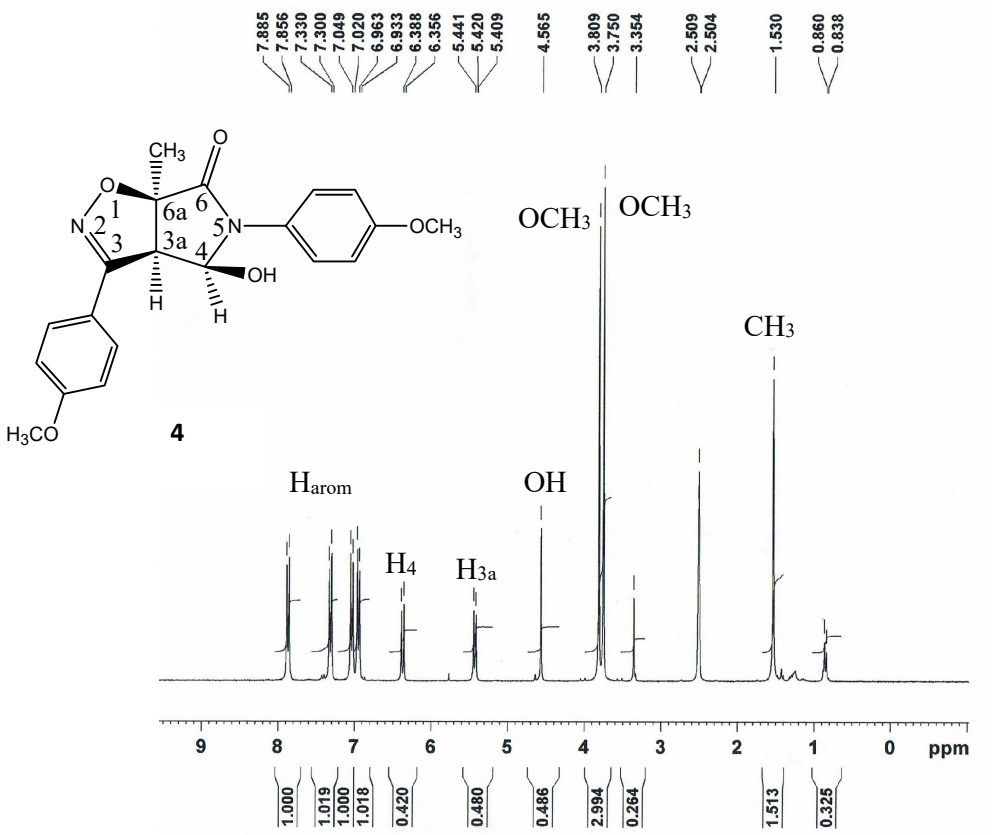


Figure 5: ^{1}H-NMR spectrum of isoxazoline 4

The ^{13}C-NMR spectra of **4** show a peak at 166.6 ppm, belonging to the carbonyl carbon (C6). The aromatic carbons are located from 114.1 to 166.6 ppm. The two peaks at 60.3 ppm and 87.9 ppm belong to C3a and C4, respectively (figure 6).

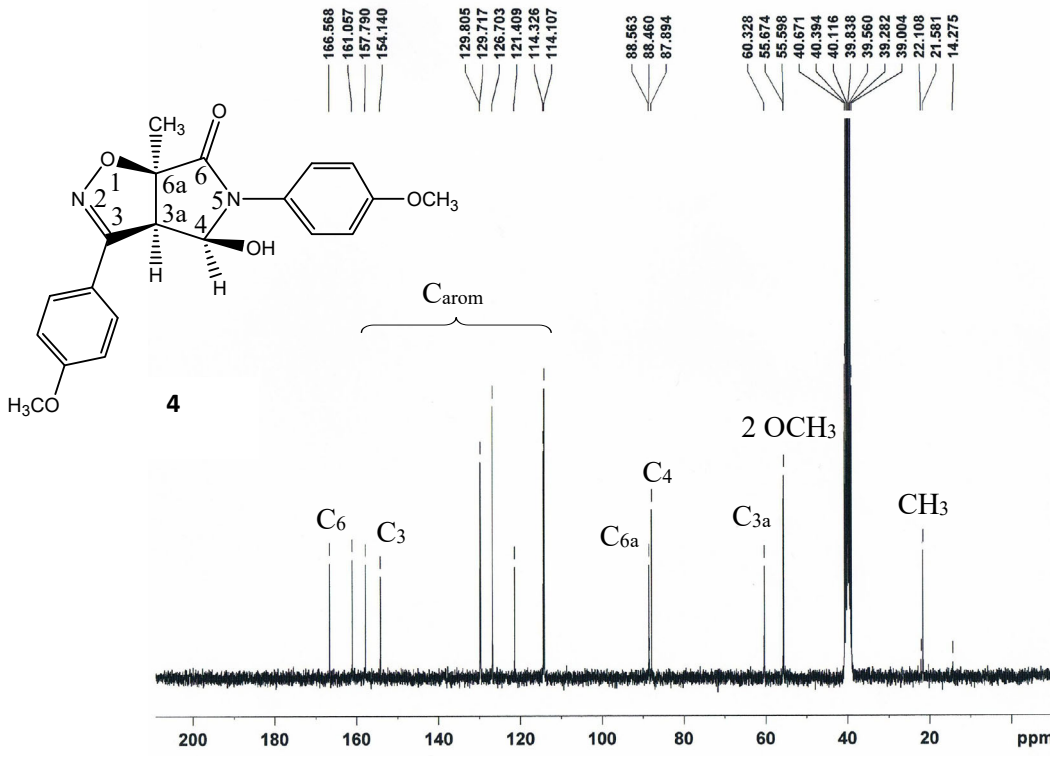


Figure 6: ^{13}C-NMR spectrum of isoxazoline 4

CONCLUSION

Conclusion

The reaction of *p*-methoxybenzonitrile oxide with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one has been studied.

1,3-dipolar cycloaddition of *p*-methoxybenzonitrile oxide with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one is taking place regiospecifically.

The molecular structure of isoxazoline was determined by ^{1}H NMR and ^{13}C NMR.

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