SYNTHESIS OF NEW CARBAMOYL SUBSTITUTED INDOLIZINES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

GÜNNUR İPEK

SEPTEMBER 2010

SYNTHESIS OF NEW CARBAMOYL SUBSTITUTED INDOLIZINES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

by

GÜNNUR İPEK

THESIS SUBMITTED TO

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

OF

THE ABANT İZZET BAYSAL UNIVERSITY

IN PARTICULAR FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER SCIENCE IN THE DEPARTMENT OF CHEMISTRY

SEPTEMBER 2010

Approval of the Graduate School of Natural and Applied Sciences

Prof. Dr. Nihat ÇELEBİ
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science

Prof. Dr. Çetin BOZKURT
Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

Prof. Dr. Nihat ÇELEBİ
Supervisor

Examining Committee Members

1- Prof. Dr. Lemi TÜRKER .....

2- Prof. Dr. Nihat ÇELEBİ .....

3- Prof. Dr. Özdemir ÖZARSLAN .....

ABSTRACT

SYNTHESIS OF NEW CARBAMOYL SUBSTITUTED INDOLIZINES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

İPEK, Günnur

M.Sc. , Department of Chemistry

Supervisor : Prof. Dr. Nihat ÇELEBİ

September 2010, 129 pages

This study focused on two important issues. Preparation and study of N-substituted 8-Hydroxyquinoline derivatives for cycloaddition reactions was the first of these issues. The second issue of the actual scope of the thesis was synthesis of new carbamoyl substituted indolizines via 1,3-dipolar cycloaddition reactions of azomethine ylides. Four types of azomethine ylides were prepared in situ from pyridinium chlorides which were tested with various olefinic and acetylenic dipolaraphiles such as dimethyl acetylenedicarboxylate, diethyl

acetylenedicarboxylate, vinyl acetate, diphenyl acetylene and phenyl acetylene. Theoretical calculations of HOMO, LUMO energy levels of both azomethine ylides and dipolaraphiles constituted an important part of this work. Based on the most resent studies literature, six new carbamoyl substituted indolizines, which were purified by means of thin layer chromatography, were synthesized. The structures of new carbamoyl substituted indolizines were elucidated by means of IR, NMR and physical characteristics (melting points and retardation factors).

Keywords : 1,3-Dipolar cycloaddition reactions, N-substituted 8-hydroxyquinoline, azomethine ylide, carbamoyl substituted indolizine

ÖZET

YENİ KARBAMOİL SÜBSTİTÜE İNDOLİZİNLERİN AZOMETİN İLİDLERİN 1,3-DİPOLAR HALKASAL KATILMA REAKSİYONLARI ÜZERİNDEN SENTEZİ

İPEK, Günnur

Yüksek Lisans Tezi , Kimya Bölümü

Tez Danışmanı : Prof. Dr. Nihat ÇELEBİ

Eylül 2010, 129 sayfa

Bu çalışmada iki önemli konu üzerine odaklanıldı. Bu konulardan ilki N-sübstitüe 8-hidroksikinolin türevlerinin halkasal katılma reaksiyonları için hazırlanması ve çalışılmasıydı. Tezin gerçek kapsamını oluşturan ikinci konu ise yeni karbamoil sübstitüe indolizinlerin azometin ilidlerin 1,3-dipolar halkasal katılma reaksiyonları üzerinden senteziydi. Piridinyum kloridlerden hazırlanan dört çeşit azometine ilid çeşitli olefinik ve asetilenik dipolarofil reaktifler olan dimetil asetilendikarboksilat, dietil asetilendikarboksilat, vinil asetat, difenil asetilen ve fenil asetilen ile test edildi.

Azometin ilidler ve dipolarafillerin HOMO, LUMO enerji seviyelerinin teorik hesaplamaları bu çalışmanın önemli bir kısmını oluşturdu. En son yapılan literatür çalışmaları baz alınarak 6 adet yeni, ince tabaka kromatografisi ile saflaştırılmış karbamoil sübstitüe indolizin sentezlendi. Bu yeni sentezlenen indolizinlerin yapı tayinleri IR, NMR ve bazı fiziksel sabitlere (erime noktası, Rf değerleri) bağlı olarak gerçekleştirildi.

Anahtar Kelimeler : 1,3-Dipolar halkasal katılma reaksiyonları, N-sübstitüe 8-Hidroksikinolin, azometin ilid, karbamoil sübstitüe indolizin

TO MY MOST SPECIAL HERO TALE

ACKNOWLEDGEMENTS

I would like to express my deep sense of gratitude to my supervisor Prof. Dr. Nihat ÇELEBİ, who has helped me a lot to learn and think more about chemistry. I thank him for his constant encouragements, excellent guide, sincere advice and endless support during all the tough times of my M.Sc. life. I do sincerely acknowledge the freedom rendered to me by him for independent thinking, executing the research and emboldening not to be daunted whenever I make a mistake. It has been definitely a privelege and pleasure to work for him.

I would like to express my special thank to Berrak ÇELEBİ for FT-IR Spectra measurements and most importantly, cordial approach towards me.

I would also like to special thank Assoc. Prof. Dr. F. Devrim ÖZDEMİRHAN for NMR data.

I would like to thank Dr. Dilek METE, Dr. Cevher ALTUĞ, Dr. Muhammet YILDIRIM, Dr. Erol AKPINAR, Dr. Elif Berna OLUTAŞ, Canan SAPMAZ, Akın SAĞIRLI, Hamza KARAKUŞ, Sibel NAÇ, Nazangül ÜNAL, E. Özge GÖZLÜKAYA, Ali YILMAZ, Hatice KARADENİZ, and of course, Metin ALKAN for their support whenever I need it.

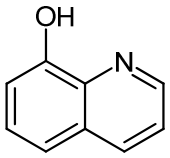
My special thanks go to Ceren ÖZÇAKIR, who is the foremost at the point of incredible patience to me everytime being always by my side however negations we live, Özlem İLKİN, Derya ÇELİK, Yağmur RAVLI, Derya ÇETİNKAYA, and Birgül GÜNER for their unconditional friendships.

In particularly I am thankful to Ferah İKİZLERLİ, Özge SARIYILDIZ BAYRAMOĞLU, Nilgün ÇEKMEZ BİNGÖL and of course, Dr: Nezir KORKMAZ for their great contribution to my life.

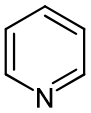
I would like to express my deepest appreciaton to my parents especially, my mother, my grandmother and my grandma for being not to let be shared out their girl everytime, their eternal love and boundless support materially and morally throughout my entire education.

Undoubtedly, one of my most special thanks goes to my father who is the most special hero tale in my life. I myself have always lived with you felt very special and thank you for all this feelings to the people in my life.

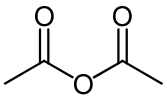
FORMULAE



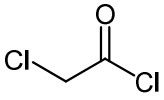
(1a)



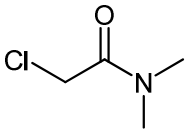
(1b)



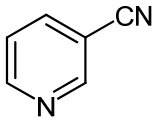
(1c)



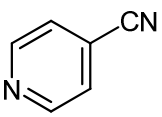
(1d)



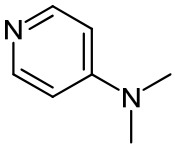
(1e)



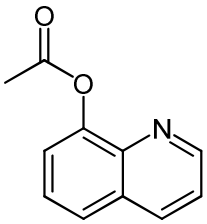
(1f)



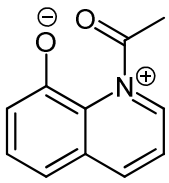
(1g)



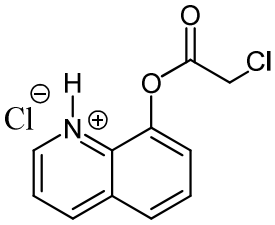
(1h)



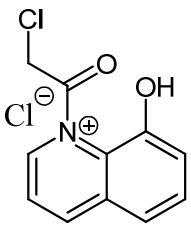
(2a)



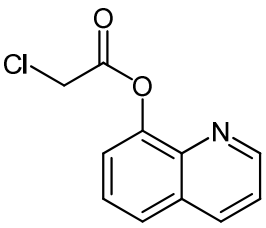
(2b)



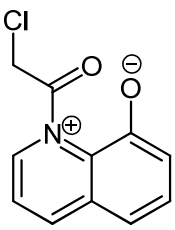
(2c)



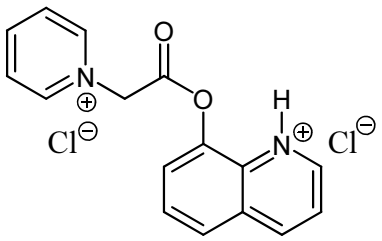
(2d)



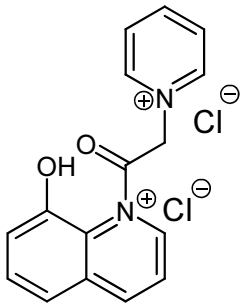
(2e)



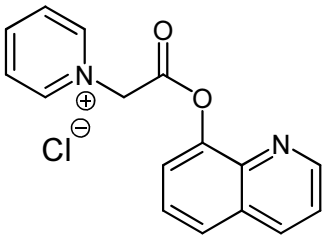
(2f)



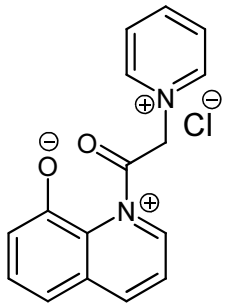
(2g)



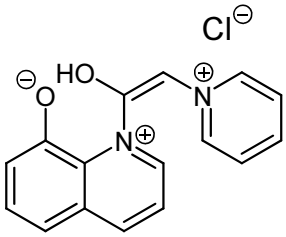
(2h)



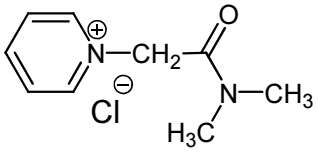
(2j)



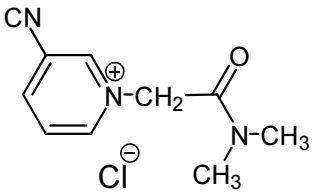
(2k)



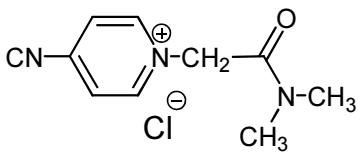
(2l)



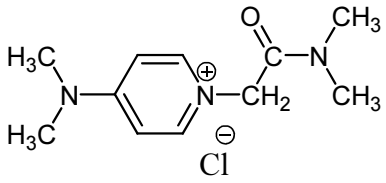
(3a)



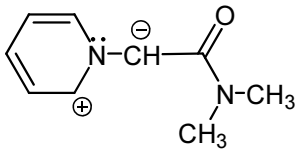
(3b)



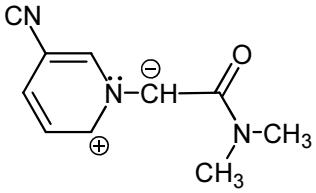
(3c)



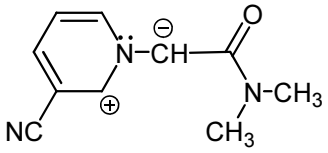
(3d)



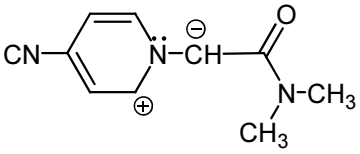
(4a)



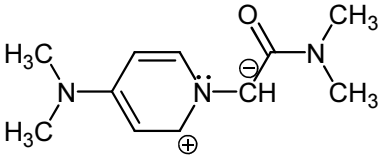
(4b)



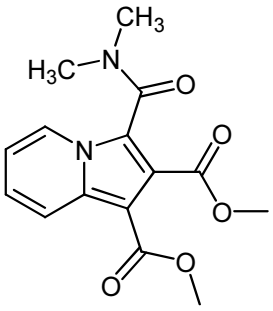
(4b')



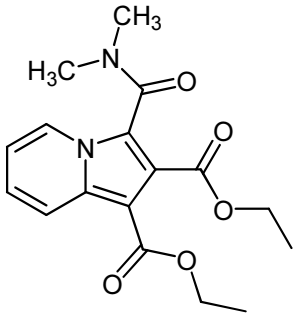
(4c)



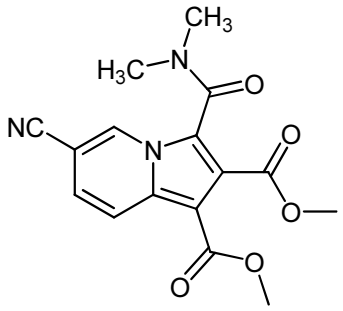
(4d)



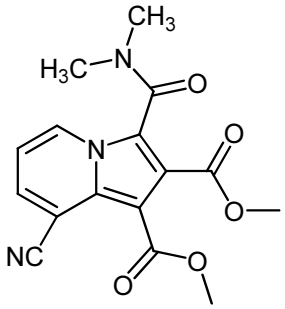
(5a)



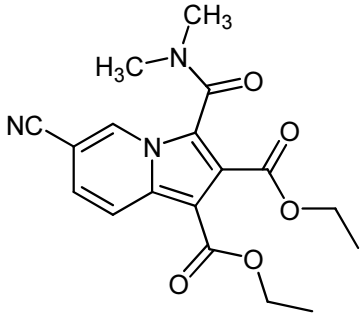
(5b)



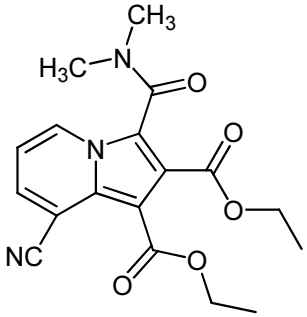
(5c)



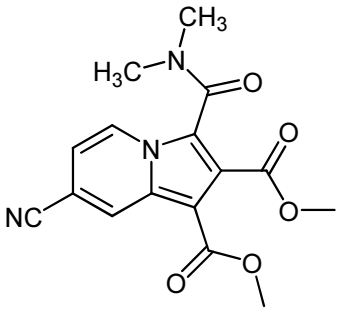
(5c')



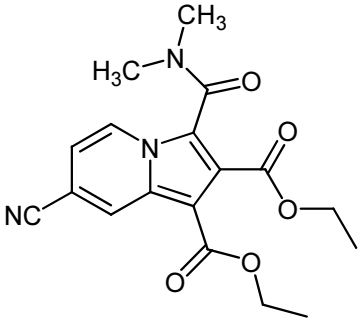
(5d)



(5d')



(5e)



(5f)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

DC	Dipolar Cycloaddition
Δ	Heat
LUMO	Lowest Unoccupied Molecular Orbital
HOMO	Highest Unoccupied Molecular Orbital
AM1	Austin Model 1
PM3	Parameterized Model 3
LCAO	Linear Combination of Atomic Orbitals
EH	Extended Huckel
MO	Molecular Orbitals
FMO	Frontier Molecular Orbitals
PMO	Perturbational Molecular Orbital
EWG	Electron Withdrawing Group
EDG	Electron Donating Group
M.p.	Melting Point

R_f	Retardation Factor
DMAD	Dimethyl acetylenedicarboxylate
DEAD	Diethyl acetylenedicarboxylate
VA	Vinyl Acetate
DPA	Diphenyl acetylene
PA	Phenyl acetylene
DMF	Dimethylformamide
EtOAc	Ethyl acetate
FT-IR	Fourier Transform Infra-Red
IR	Infra Red
NMR	Nuclear Magnetic Resonance
J	Coupling Constant
s	singlet (NMR)
t	triplet (NMR)
d	doublet (NMR)
dd	doublet of doublets (NMR)
m	multiplet (NMR)
ppm	Parts per million (NMR)
Hz	Hertz

1. INTRODUCTION

1.1. THEORY OF CONCERTED REACTIONS

Reactions in which more than one bond is broken or formed can be divided into two classes [1].

1. Those in which all bonds are broken and new ones are formed simultaneously so that no intermediates are involved. Such reactions are called concerted or multicentre reactions because the changes occur in concert or at the same time at more than one center. In such processes there is only one energy barrier and one transition state.

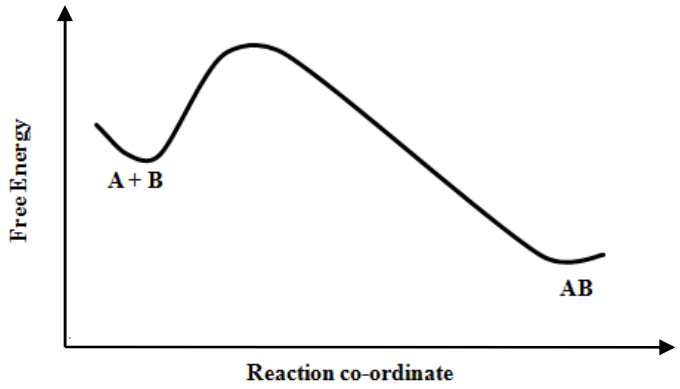


Figure 1. 1 Energy profile of a Concerted Mechanism

2. This class includes reactions in which the bond forming and bond breaking processes other consecutively so that one or more intermediates are involved. These intermediates may be highly stable and capable of isolation or they may be reactive species of only transient existence.

When the intermediate is stable, it is convenient to regard the entire process as consisting of two or more consecutive concerted processes. But where the intermediates are unstable, the entire process is regarded as one reaction which proceeds in a stepwise manner.

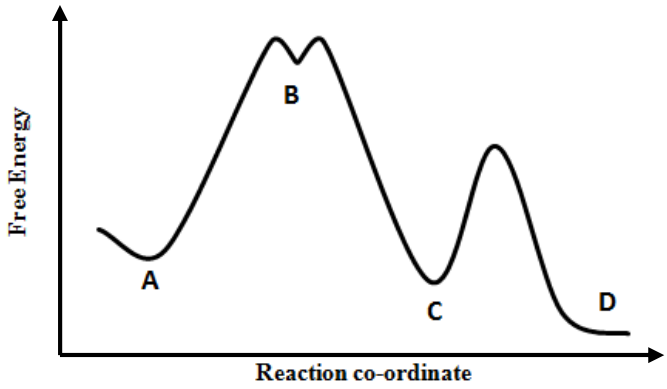


Figure 1. 2 Energy profile of a Stepwise Mechanism

In such a reaction C is formed from A via an unstable intermediate B which has a short life time. Since B lies in a shallow energy well, it is unstable. It has a small energy barrier to surmount by which if can pass on to the products or it can revert to the reactants. The more stable an intermediate is, the deeper is the energy well, so C is relatively more stable than B.

1.1.1. Concerted Mechanism

Let us take a reaction in which a cyclic transition state is formed.

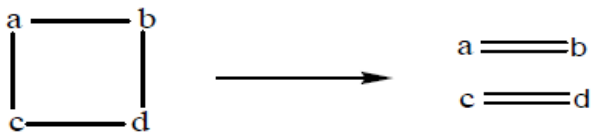


Figure 1. 3 A hypothetical fragmentation of a ring

In the concerted fragmentation, the breaking of the *a*—*c* and *b*—*d* bonds are going on at the same time. The overall reaction does not involve an intermediate. There is only one energy barrier in which both σ bonds are partially broken and new π *a* = *b* and *c* = *d* bonds are partially formed.

When the two σ bonds break simultaneously and at an exactly the same rate, it is called a synchronous process. If, however the reactant is unsymmetrical, the two σ bonds do not break at the same rate. In 1969 R.B. Woodward and R. Hoffmann developed a general theory of concerted reactions which proceed through a cyclic transition state process which they turned *pericyclic*. They used the concept of orbital symmetry to predict which types of cyclic transition state are energetically feasible.

1.1.2. Stepwise Mechanism

If the two σ bonds *a*—*c* and *b*—*d* break in two successive independent steps, then we have an intermediate in which only one of the σ bonds is broken and the energy profile will be as in Figure 1.2, with two transition states.

The intermediates fall into two categories:

(i) Those which are highly polar

(ii) Those which are essentially non-polar

1.2. Pericyclic Reactions

In 1969 R.B. Woodward and R. Hoffmann introduced the term pericyclic reactions to differentiate those reactions which have a [1, 2]

(*i*) a common cyclic transition state;

(*ii*) are highly stereospecific; and

(*iii*) their stereochemistry depending on the total number of π and σ electrons involved in the formation or breaking of bonds.

Thus pericyclic reactions are intra or intermolecular processes which involve concerted reorganisation of electrons within a closed loop of interacting orbitals. Six classes of pericyclic reactions have been recognized [3].

- Cycloaddition reactions
- Sigmatropic reactions
- Electrocyclic reactions
- Cheletropic reactions
- Group transfer reactions
- Dyotropic reactions

1.2.1. Cycloaddition Reactions

A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a cycloaddition reaction [4]. The number of participating π-electrons in each component is given in brackets preceding the name, and the reorganization of electrons may be depicted by a cycle of curved arrows - each representing the movement of a pair of electrons. The major cycloaddition reactions are Diels-Alder reaction a [4+2] cycloaddition and, the 1,3-dipolar cycloaddition a [3 + 2]cycloaddition. This type of reaction is non-polar addition reaction.

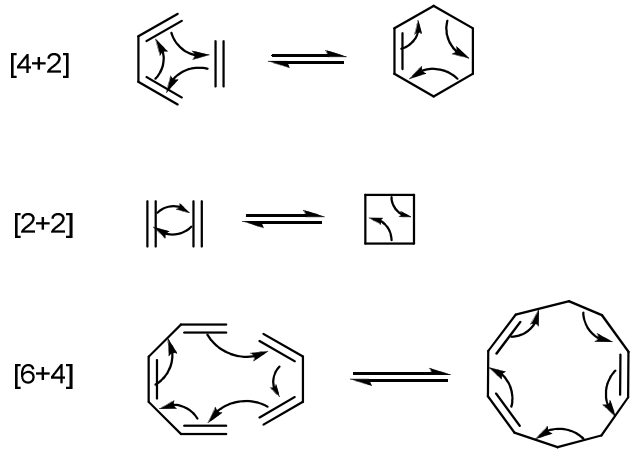


Figure 1. 4 A simple representation of Cycloaddition Reactions

According to the Huisgen a cycloaddition reaction has to fulfill with the following requirements [5].

i) Cycloadditions are ring closures in which the number of σ-bonds increases.

ii) Cycloadditions are not associated with the elimination of small molecules or ions. The cycloadduct corresponds to the whole integrity of the components.

iii) Cycloadditions do not involve the cleavage of σ-bonds. The reverse is true for retroadditions.

iv) Cycloadditions can be intramolecular, if a molecule contains the necessary number of π-bonds (σ-bonds for retroadditions) in its skeleton.

v) When more then two components combine, only the reaction step leading to the ring formation is a cycloaddition.

vi) The products of a cycloaddition need not be stable, or isolable, but the cycloadducts must occur at least as intermediates.

1.2.2. Sigmatropic Reactions

Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called sigmatropic reactions. The total number of σ-bonds and π-bonds remain unchanged. These rearrangements are described by two numbers set in brackets, which refer to the relative distance (in atoms) each end of the σ-bond has moved.

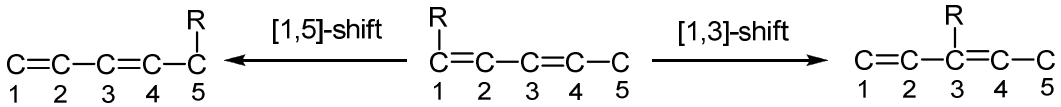


Figure 1. 5 A simple representation of Sigmatropic Reactions

1.2.3. Electrocyclic Reactions

In organic chemistry, an electrocyclic reaction is a type of pericyclic rearrangement reaction where the net result is one pi bond being converted into one sigma bond or vice-versa. These reactions are usually unnamed, being categorized by the following criteria [2]:

- electrocyclic reactions are photoinduced or thermal
- the number of pi electrons in the species with more pi bonds determines reaction mode
- electrocyclic reaction can be a ring closure (electrocyclization) or a ring opening reaction
- the stereospecifity is determined by conrotatory or disrotatory mode of transition state formation as predicted by the Woodward-Hoffmann rules.

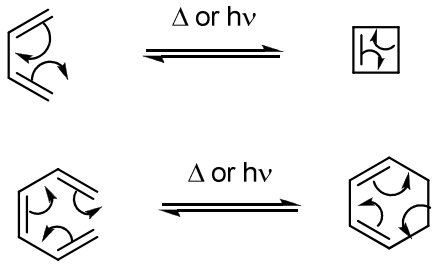


Figure 1. 6 A simple representation of Electrocyclic Reactions

1.2.4. Cheletropic Reactions

Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions. Two bonds are formed or broken at a single atom. The nomenclature for cheletropic reactions is the same as for cycloadditions.

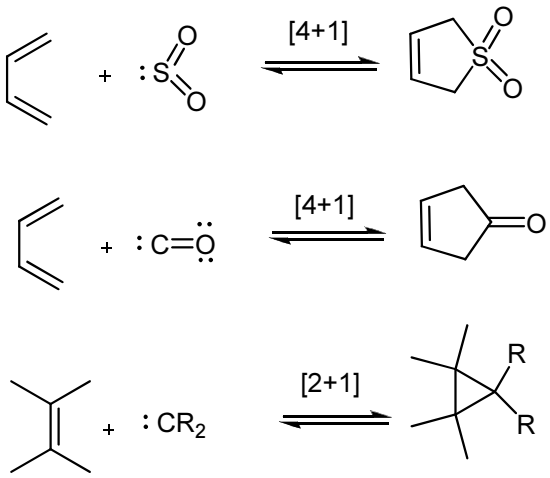


Figure 1. 7 A simple representation of Cheletropic Reactions

1.2.5. Group Transfer Reactions

Group transfer reactions are pericyclic reactions where one pi bond is converted to one sigma bond, at the same time that a sigma bond migrates.The best known group transfer reaction is the ene reaction.

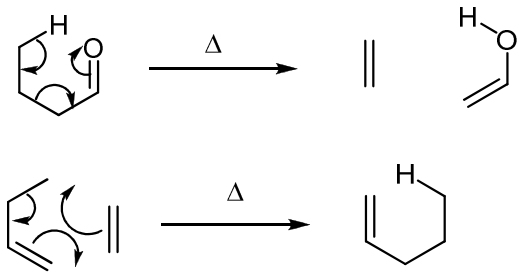


Figure 1. 8 A simple representation of Group Transfer Reactions.

1.2.6. Dyotropic Reactions

A Dyotropic Reaction in organic chemistry is a type of organic reaction and more specifically a pericyclic valence isomerization in which two sigma bonds simultaneously migrate intramolecularly [6]. The reaction type is of some relevance to organic chemistry because it can explain how certain reactions occur and because it is a synthetic tool in the synthesis of organic molecules for example in total synthesis. It was first described by Manfred T. Reetz in 1971 [7, 8].

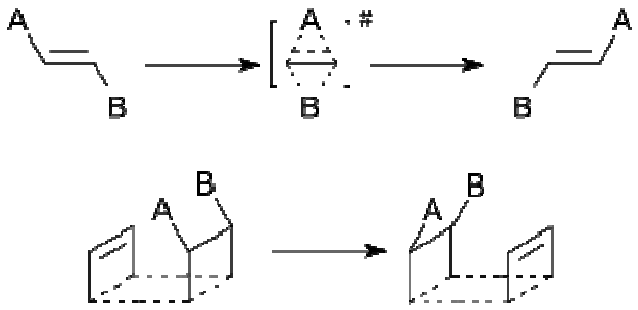
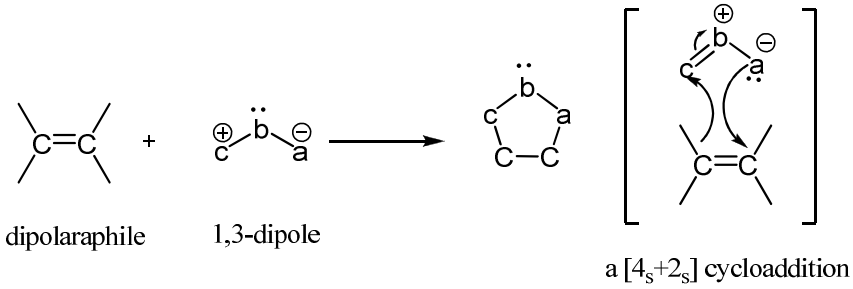


Figure 1. 9 A simple representation of Dyotropic Reactions.

1.3. 1,3-DIPOLAR CYCLOADDITION REACTIONS

The 1,3-dipolar cycloaddition reaction is the single most important method for the construction of heterocyclic five-membered rings in organic chemistry [9, 10]. The 1,3-dipolar cycloaddition reactions are used for the preparation of molecules of fundamental importance for both academia and industry [11]. The general application of 1,3-dipoles in organic chemistry was first established by the systematic studies by Huisgen in the 1960s [12]. At the same time, the new concept of conservation of orbital symmetry, developed by Woodward and Hoffmann [13, 14].



Scheme 1. 1 The simple representation of a 1,3-dipolar cycloaddition.

The development of the 1,3-dipolar cycloaddition reactions has in recent years entered a new stage as control of the stereochemistry in the addition step is now the major challenge. The stereochemistry of these reactions may be controlled either by choosing the appropriate substrates or by controlling the reaction using a metal complex acting as catalyst [15].

1.3.1. The 1,3-Dipoles

The “1,3-dipole” is defined as a species which is represented by zwitterionic resonance structures and which undergoes 1,3 cycloadditions to a multiple bond system, the “dipolaraphile” [16]. The 1,3-dipole consists of elements from main groups IV, V, and VI. The parent 1,3-dipoles consists of elements from the second row and the central atom of the dipole is limited to N or O [17]. Thus, a limited number of structures can be formed by permutations of N, C, and O.

Dipolar cycloaddition reactions take place between unsaturated hetero atom compounds, such as diazoalkanes, alkyl and aryl azides, nitrile oxides and nitrones, and alkene or alkyne functions. Although the former reactants are neutral, their Lewis structures have formal charges, and may be written as 1,3-dipoles. The terminology used for these reactions may be confusing unless one pays careful attention to the electronic structures of the dipolar reactants. The 1,2-dipolar structures retain valence shell octets for all heavy atoms, suffer less charge separation, and have one more covalent bond than do the 1,3-dipolar structures. Therefore, the most representative Lewis structures for these compounds are 1,2-dipoles, not 1,3-dipoles. Another factor in identifying the best structure for a given compound is electronegativity. Negative charge is best on the most electronegative atom, and positive charge on the least electronegative atom.

Basically, 1,3-dipoles can be divided into two different types: the allyl anion type and the propargyl/allenyl anion type. (Figure 1.10)

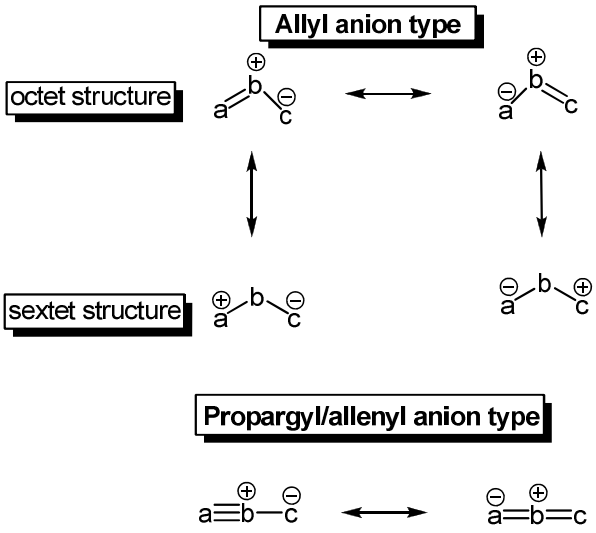


Figure 1. 10 Charge distribution of allyl anion and propargyl/allenyl anion type of 1,3 dipoles.

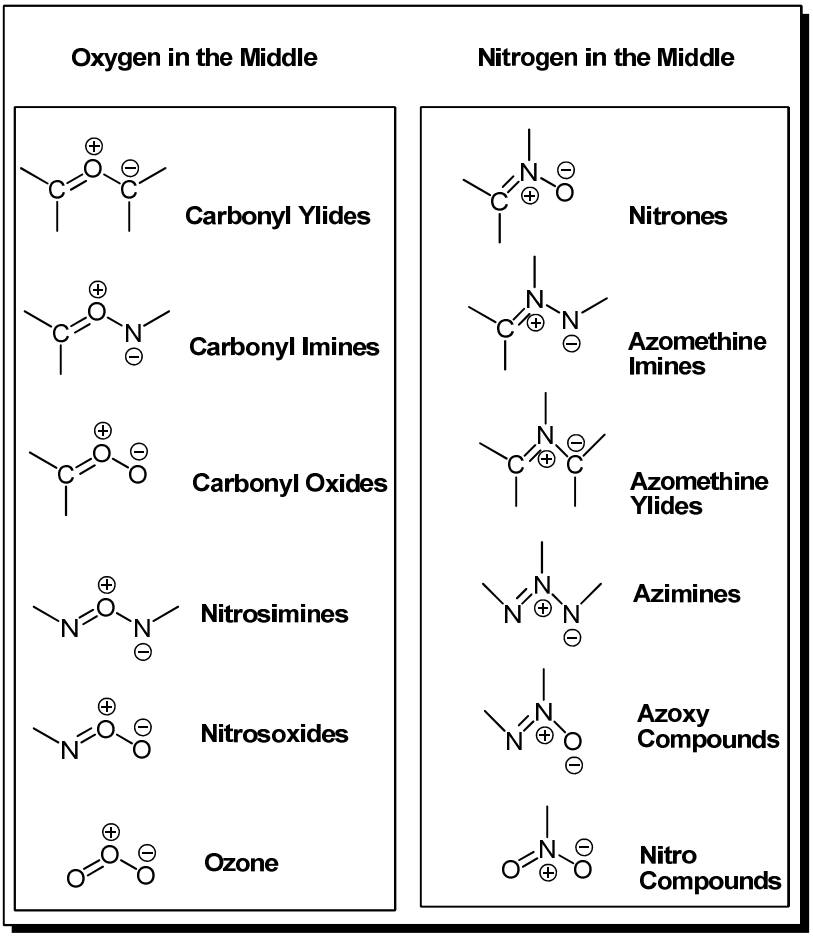


Figure 1. 11 Allyl anion type of 1,3-dipoles

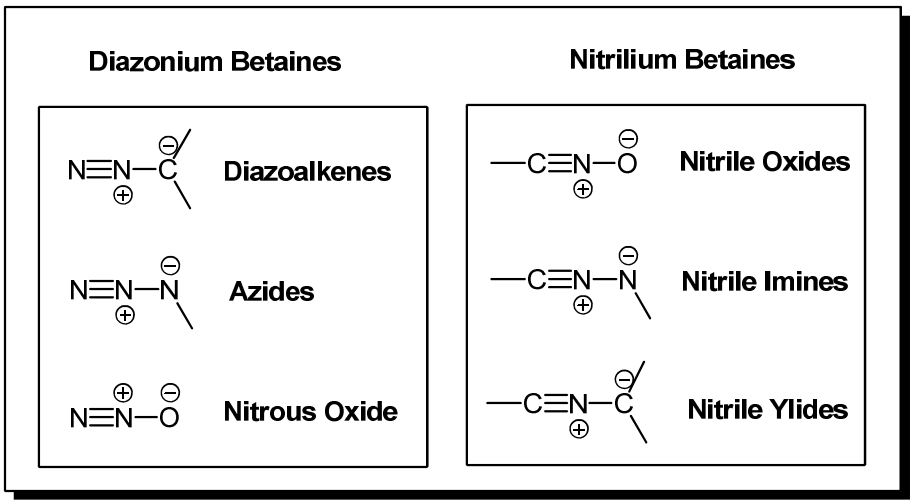


Figure 1. 12 Propargyl/allenyl anion type of 1,3-dipoles.

In the propargyl-allenyl type, b atom must be nitrogen. No other element has an extra pair of electrons available while remaining in the triply bonded neutral state. In the allyl type, b atom can be occupied by either a nitrogen or an oxygen atom [18].

1.3.2. The Dipolaraphiles

An unsaturated system that undergoes 1,3-DC with 1,3-dipoles is called dipolarophile. Alkenes, alkynes, and their diverse hetero derivatives may react as dipolarophiles. Generally electron deficient dipolarophiles role model as dipolarophiles in 1,3-DC reactions. Specific examples to generally used electron deficient dipolarophiles can be given as: α,β-unsaturated carbonyl compounds (**7**), allylic alcohols (**8**), allylic halides (**9**), alkynes (**10**), vinylic ethers (**11a**), vinylic esters (**11b**), imines (**12**), and ketones (**13**) [19].

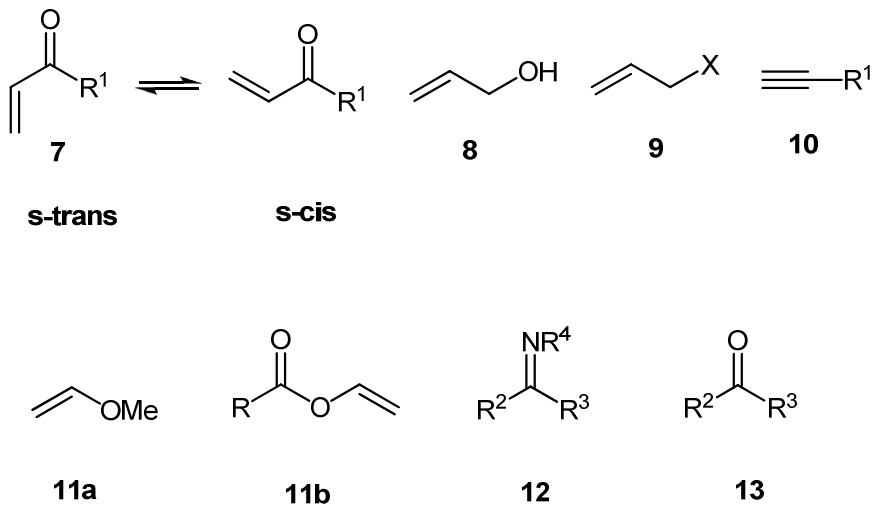
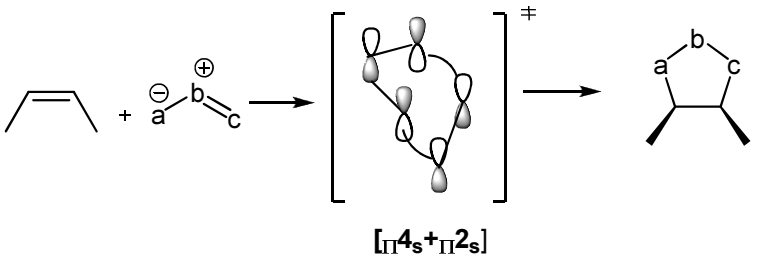


Figure 1. 13 Various C-C, C-N and C-O Dipolarophiles Used in 1,3-Dipolar Cycloadditions.

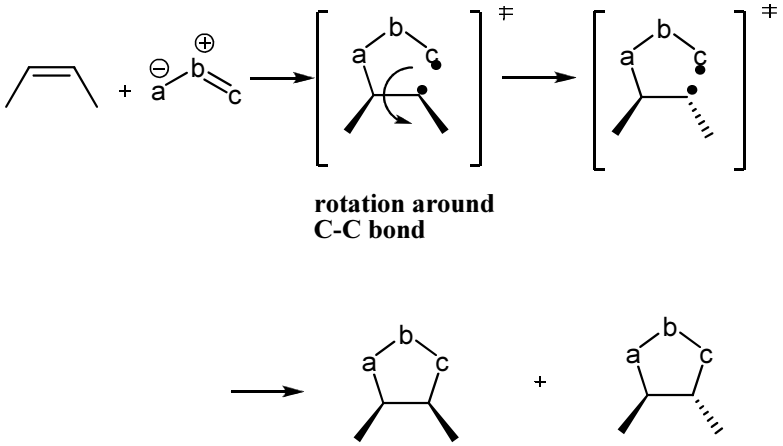
1.3.3. Mechanistic Approaches to 1,3-Dipolar Cycloaddition Reactions

As a conclusion of serious collection of experimental data, Huisgen et al. claimed that, 1,3-DC reactions proceed through a concerted mechanism, which means that all the bonds were created simultaneously, but not necessarily to the same extent at a certain time [12, 20].

concerted mechanism



singlet diradical mechanism

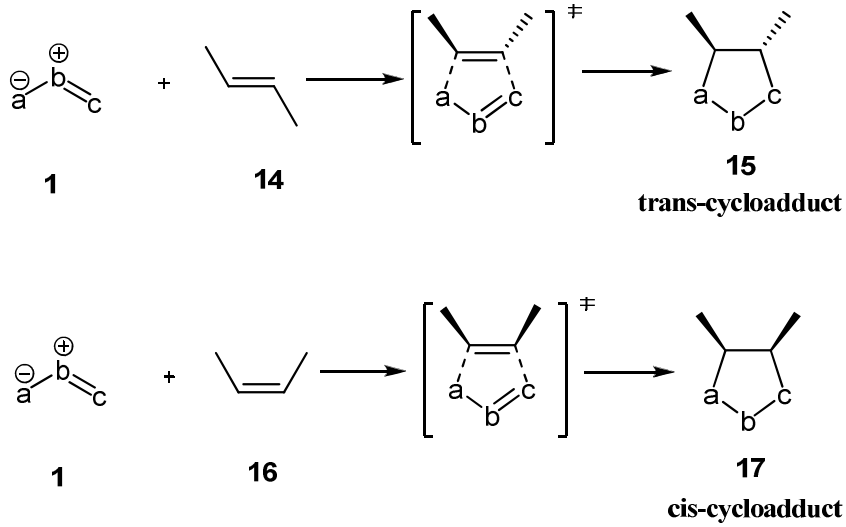


Scheme 1. 2 Concerted versus singlet diradical mechanisms of 1,3-DC reactions

Firestone et al. claimed that, the 1,3-DC reaction proceeds through a singlet diradical intermediate. When *cis*- or *trans*-alkene is used, a 180° rotation of the C-C bond is possible in this diradical intermediate and thus be expected to yield a mixture of the *cis*- and *trans*- isomers of the cycloadduct.

According to the Woodward-Hoffmann rules [13,14], 1,3-DC reaction proceeds over concerted mechanism and thermally allowed with the description of [$_{\pi}4_{s}$ + $_{\pi}2_{s}$]. This means that the three pz orbitals of the 1,3-dipole and the two pz orbitals of the dipolarophile both combine suprafacially.

In concerted 1,3-DC reaction, the stereochemistry of the dipole and the dipolarophile are retained in the final product. This is exemplified in Scheme 1.3, where the dipolarophile *trans*-2-butene **14** reacts with the hypothetical dipole **1** furnishing exclusively *trans*-cycloadduct **15**. Starting from the *cis* alkene **16** will thus yield only the *cis*-cycloadduct **17**. (Scheme 1.3)



Scheme 1. 3 Retaining the stereochemistry of dipolarophile during a concerted 1,3-DC reaction.

1.3.4. Frontier Molecular Orbital Interactions

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals (FMO) of the substrates. The $LUMO_{dipole}$ can interact with the $HOMO_{dipolarophile}$ and the $HOMO_{dipole}$ with the $LUMO_{dipolarophile}$. [13,14,21,22]. Sustmann has classified 1,3-dipolar cycloaddition reactions into three types, based on the relative FMO energies between the dipole and the dipolaraphile [23,24,25].

Type I comprises the reactions controlled by the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction, or so called normal-electron demand (NED) reactions. Processes governed by the $HOMO_{dipolarophile}$-$LUMO_{dipole}$ interaction, or the so-called inverse-electron-demand (IED) reactions, form Type III. If the energies of the valance MOs of two reactants are similar, the reaction is controlled by both types of the HOMO-LUMO interaction. The processes belong to type II (Figure 1.14).

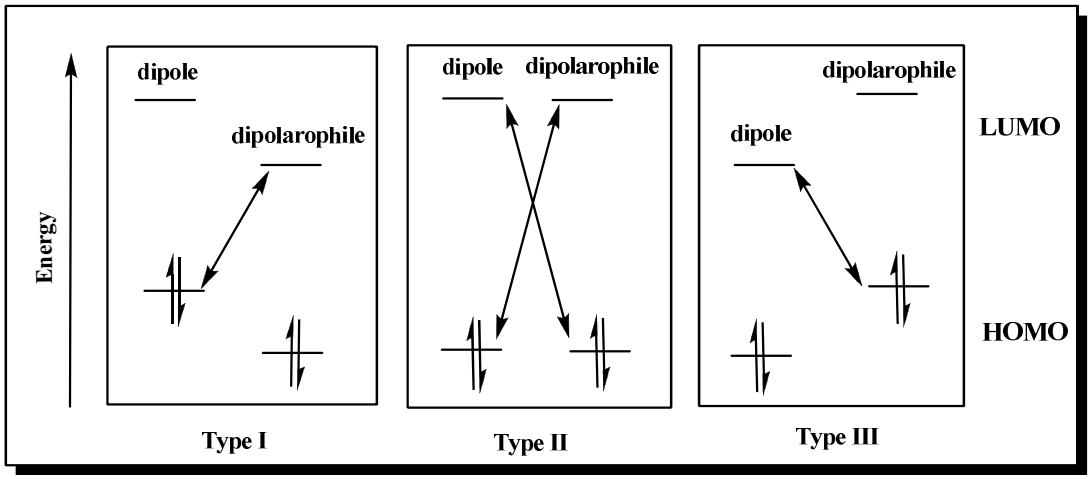


Figure 1. 14 The classification of 1,3-DC reactions on the basis of the FMOs: type I, a $HOMO_{dipole}$-$LUMO_{alkene}$ interaction; type II, interaction of both $HOMO_{dipole}$-$LUMO_{alkene}$ and $LUMO_{dipole}$-$HOMO_{alkene}$; type III, a $LUMO_{dipole}$-$HOMO_{alkene}$ interaction.

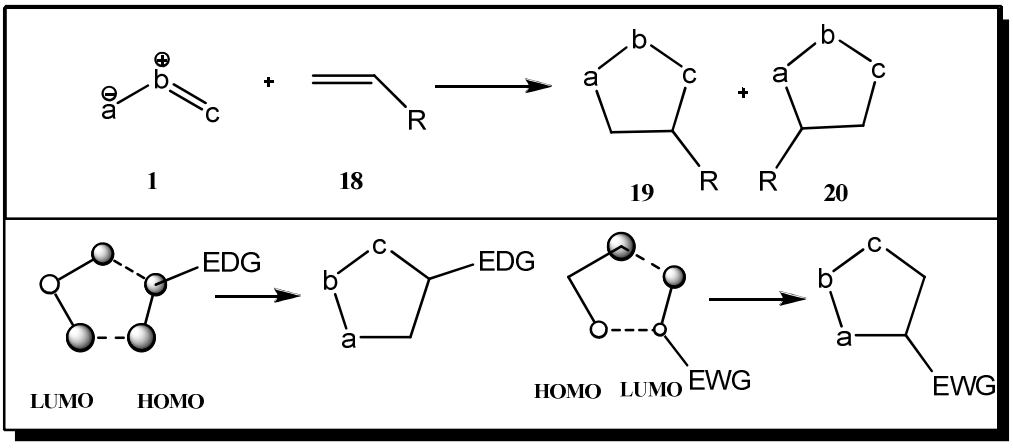
1,3-DC reactions of type I are typical for substrates such as azomethine ylides and azomethine imines, while reactions of nitrones are normally classified as type II. 1,3-DC reactions of nitrile oxides are also classified as type II, but they are better classified as borderline to type III, since nitrile oxides have relatively low lying HOMO energies. Examples of type III interactions are 1,3-DC reactions of ozone and nitrous oxide.

1.3.5. The Selectivities of 1,3-Dipolar Cycloaddition Reactions

Depending upon the presence of substituents (electron donating or electron withdrawing) on dipole and dipolarophile, the FMO energies and as a result the type of 1,3-DC reactions may change.

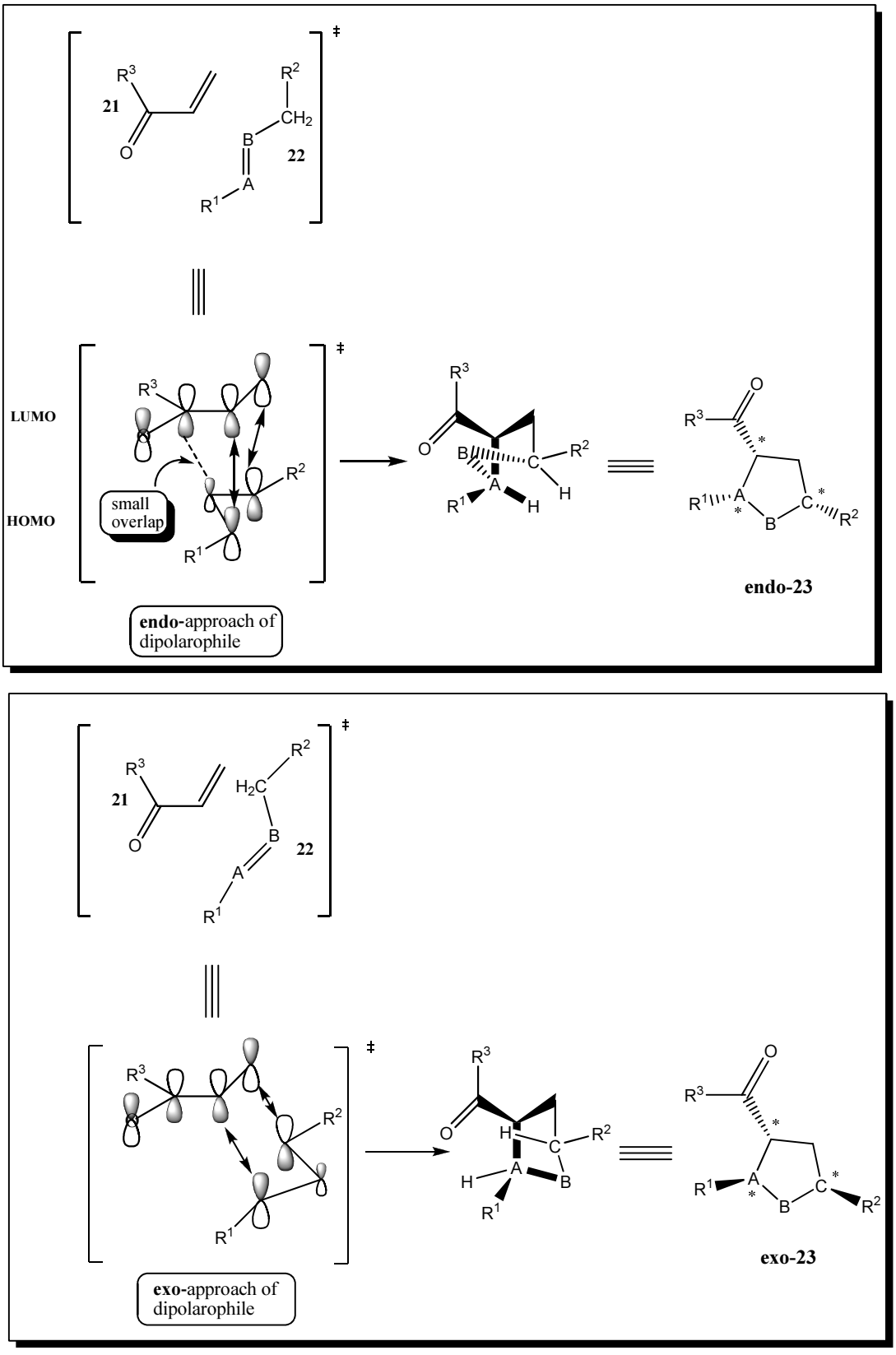
For example, when methyl acrylate reacts with *N*-methyl-*C*-phenylnitrone, the reaction is controlled by the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction (type I). However, the reaction of methyl vinyl ether with the same nitrone is controlled by the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction (type III). As it has been seen in this example, substituents influence and perturb the FMO energies of the dipolarophile. Additionally, the perturbation of FMO energies of reactants may effect the selectivity of the reaction. Three types of selectivity must be considered in 1,3-dipolar cycloaddition reactions-regioselectivity, diastereoselectivity¸ and enantioselectivity. The regioselectivity is controlled by steric and electronic effects [26].

However, the electronic properties of the substrates sometimes predominate in terms of selectivity, and the atom with the largest HOMO in the dipole interacts with the atom with the largest LUMO in the dipolarophile (Scheme 1.4).



Scheme 1. 4 Regioselectivity in 1,3-DC reactions.

It is possible that when a dipolarophile **21** reacts with an allyl anion type dipole **22**, the reaction could either go through an ***endo***- or an ***exo***-transition state and produce two diastereomeric cycloadducts, ***endo*-23** or ***exo*-23** as depicted in Scheme 1.5. It is very well known that, in Diels-Alder reaction, ***endo***- transition state is stabilized with a secondary π-orbital interaction. Here, it can be seen clearly that ***endo*** approach of the dipolarophile is stabilized by a small secondary π-orbital interaction between the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ which contributes to the ***endo***/**e*xo*** selectivity of the reaction (Type II and III).



Scheme 1. 5 Diastereoselectivity in 1,3-DC reactions. Possible ***endo***- and ***exo*** approaches involved in the reaction of dipolarophile and dipole.

1.3.6. Theoretical Background and Computational Method Used in 1,3-DC Reactions

Molecular orbital theory explains the reactivities of cycloaddition reactions by using the energy differences between the reactants and the transition states. Linear combination of atomic orbitals (LCAO) method is used in molecular orbital calculations.

Interactions between two conjugated molecules with overlapping p orbitals is described in terms of the π electrons of the separate system. The orbitals that interact have been called the frontier orbitals by Fukui [27].

Frontier orbitals are given the names, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).

The principle of conservation of orbital symmetry, explained by Fukui, Woodward and Hoffmann [13,14,28,29], provides a fruitful theoretical basis for concerted reactions.

Whether a concerted reaction is allowed or not, can be predicted by orbital symmetry rules, which are also known as Woodward-Hoffmann rules [30]. The orbital symmetry rules are related to the Huckel aromaticity. The selection rules for cycloaddition reactions can be derived from consideration of the aromaticity of the transition state. In applying the orbital symmetry, sign inversions are taken into account. System with zero and even number of sign inversions are called Huckel systems. A thermal pericyclic reaction involving a Huckel system is allowed only if the total number of electrons is 4n+2. Systems with an odd number of sign inversions are called Möbius systems, in which a thermal pericyclic reaction is allowed, if the total number of electrons is 4n. For photochemical reactions these rules are reversed [31].

In concerted reactions, if the new bonds are formed from the same face of the π system, the reaction is a suprafacial-suprafacial process. For [π 4 s+π 2 s], Diels-Alder reactions suprafacial-suprafacial process is symmetry allowed according to Woodward-Hoffmann rules [13,14]. In symmetry allowed [π 2 s+π 2 s] cyclization reactions the new σ bonds are formed from the opposite faces of the π system. This manner of bond formation is called antrafacial-suprafacial.

For the [π 4 s+π 2 s] suprafacial-suprafacial cycloaddition the transition state is aromatic, while for [π 2 s+π 2 s] suprafacial-suprafacial mode it is anti-aromatic and suprafacial-antrafacial mode is aromatic (Figure 1.19).

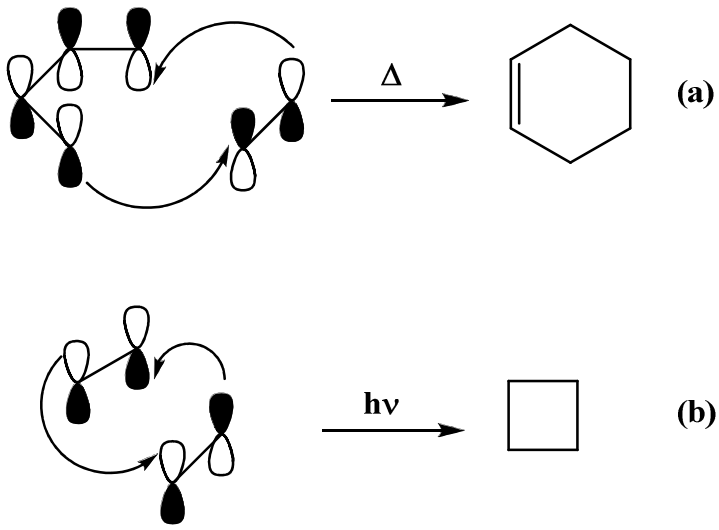


Figure 1. 15 Representation of (a) [π 4 s+π 2 s] and (b) [π 2 s+π 2 s] reactions.

As two conjugated systems approach each other along the lowest energy path, the greatest stabilization upon the interaction is provided. The magnitude of this stabilization depends upon the nature of the interacting molecular orbitals of the conjugated systems and can be estimated by using the perturbational molecular orbital (PMO) and frontier molecular orbital (FMO) theories.

The most popular semiemprical calculation methods are the Austin Model 1 (AM1) [32] and Parameterization Method 3 (PM3) [33]. Both are popular for organic compounds and use more or less the same equations but having different set of parameters.

Both provide accurate results in order to use for organic molecules that the data can easily be used for estimating their reactivities.

1.3.6.1. Perturbational Molecular Orbital Theory (PMO)

How a change in structure, perturbation, will affect the MO's can be understood by the help of PMO. In a PMO a system under analysis is compared to an another related system for which the MO pattern is known.

In molecular orbital theory, reactivity is related to the relative energies and shapes of the orbitals, which are involved during the transformation of reactants to products. The shapes of the orbitals, which affect the energy of the reactions, are quantified by atomic coefficients.

PMO incorporates the concept of frontier orbital theory, which proposed that the most important reactions between the highest molecular orbital of one reactant and the lowest molecular orbital of the other reactant.

A basic postulate of PMO theory is that the strongest overlap occurs, when the interacting orbitals, with the same sign, on two reaction centers have the highest coefficients on the participating atoms. Another postulate of PMO theory is that only MO's of matching symmetry can interact for the bond formation. Thus, relative energies and symmetry of the frontier orbitals are taken into account in PMO theory. The relative energies of the frontier orbitals can be approximated by first order perturbation theory.

$$\Delta E_u = \sum_i C_{ui}^2 \Delta\alpha_i + \sum_i \sum_j C_{ui} C_{uj} \Delta\beta_{ij}$$

The above equation, derived from the PMO approach to first order changes, indicates the change in energy of the u^{th} molecular orbital as a function of changes in Coulomb integral (electronegativity or ionization potential) and resonance integrals (bond energy). The PMO theory utilizes ground state frontier eigenvalues and eigenvectors in the second order perturbation theory and provides knowledge of the energetics of the transition state between the two participating frontier orbitals [34].

1.3.6.2. Frontier Molecular Orbital Theory (FMO)

Frontier molecular orbital theory (FMO) provides the basic framework for analysis of the effect that symmetry of orbitals has upon reactivity.
Cycloaddition reactions are allowed only when all overlaps between the HOMO of one reactant and the LUMO of the other are such that a positive lobe overlaps with another positive lobe and a negative lobe only with another negative lobe.

To apply FMO theory, the coefficients and energies of the frontier orbitals are necessary. The interaction energy between the HOMO of one reactant and the LUMO of the second is calculated by using the second order perturbation theory [35]. The total interaction energy (ΔE) is a measure of the transition state stabilization (or destabilization) in the direction of maximum overlap.

According to Fukui [35] , reactions take place in the direction of maximal HOMO-LUMO overlap. In concerted cycloadditions that orientation should be favored in which the centers with the largest atomic coefficients interact.

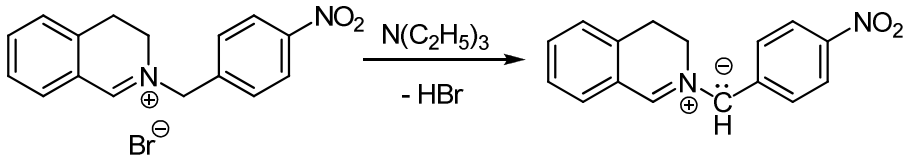
The use of these generalized frontier orbitals within the framework of qualitative perturbation molecular orbital theory provides a qualitative explanation of differential reactivity, regioselectivity and periselectivity in cycloadditions [36,37].

1.4. AZOMETHINE YLIDES

1.4.1. The History of Azomethine Ylides

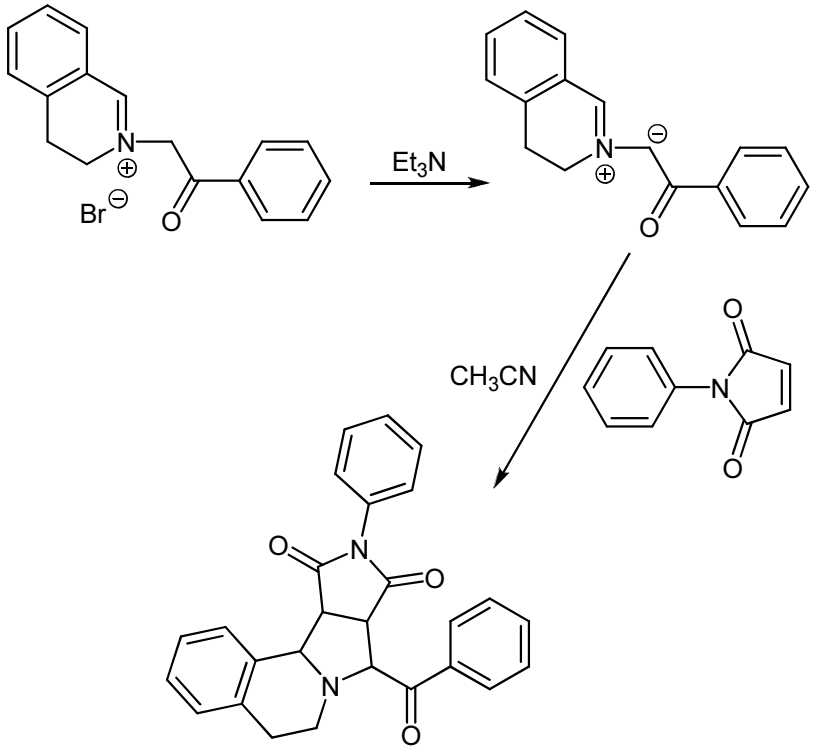
The history of 1,3-dipoles goes back to Curtius who in 1883 discovered diazoacetic ester [38]. Five years later his younger colleague Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters and described the first 1,3-DC reaction [39]. In 1893 he suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was a 1-pyrazoline and that the isolated 2-pyrazole was formed after rearrangement of the 1-pyrazole [40]. The general application of 1,3-dipoles in organic chemistry was first established by the systematic studies by Huisgen in the 1960s [12].

The first azomethine ylide was prepared from *N*-(*p*-nitrobenzyl)-3,4-dihydroisoquinolinium bromide with triethylamine in hot pyridine. This is exemplified in Scheme 1.6. It is not stable enough to be isolated but adds readily to dimethyl fumarate in situ [41].



Scheme 1. 6 An example for the synthesis of *N*-(*p*-nitrobenzyl)-3,4-dihydroisoquinolinium ylide via elimination of HBr

Another short-lived azomethine ylide, which is obtained from *N*-phenylacyl-3,4-dihydroisoquinolinium bromide with triethylamine, also undergoes cycloadditions with olefinic dipolarophiles; with *N*-phenylmaleimide in acetonitrile a 73% yield of the 1:1 adduct is obtained [41]. This synthesis is represented in Scheme 1.7.



Scheme 1. 7 Synthesis of *N*-phenylacyl-3,4-dihydroisoquinolinium ylide

The first asymmetric catalytic 1,3-dipolar cycloaddition reaction of azomethine ylides was described by Zhang and co-workers in 2002 [42]. In this reaction, the cycloaddition of the azomethine ylide and the dipolarophile with appropriate substituents proceeded in good yield and high enantioselectivity by using Trost's ligand and a catalytic amount of AgOAc as the Lewis acid. Since then, several effective complexes including Cu(II)/Ligand [43], Zn(II)/Ligand [44], and

Cu(I)/Ligand [45] have been developed to afford cycloadducts with high stereoselectivity.

1.4.2. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

Azomethine ylides are planar molecules composed of one nitrogen atom and two terminal sp^2 carbons, and have four π electrons spread over the three-atom C-N-C unit; such as they must be represented by a zwitterionic (or diradical) form. Four zwitterionic resonance forms can be drawn, as shown in Figure 1.16. The most common representation has a positive charge located on the nitrogen atom and a negative charge distributed over the two carbon atoms [20].

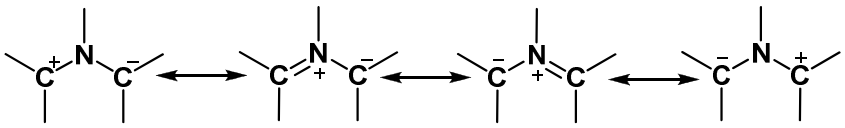
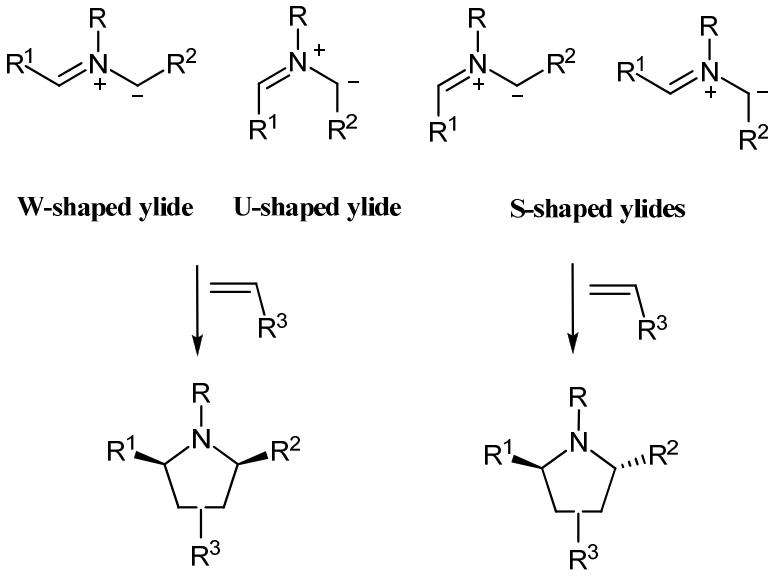


Figure 1. 16 Zwitterionic resonance forms of azomethine ylides

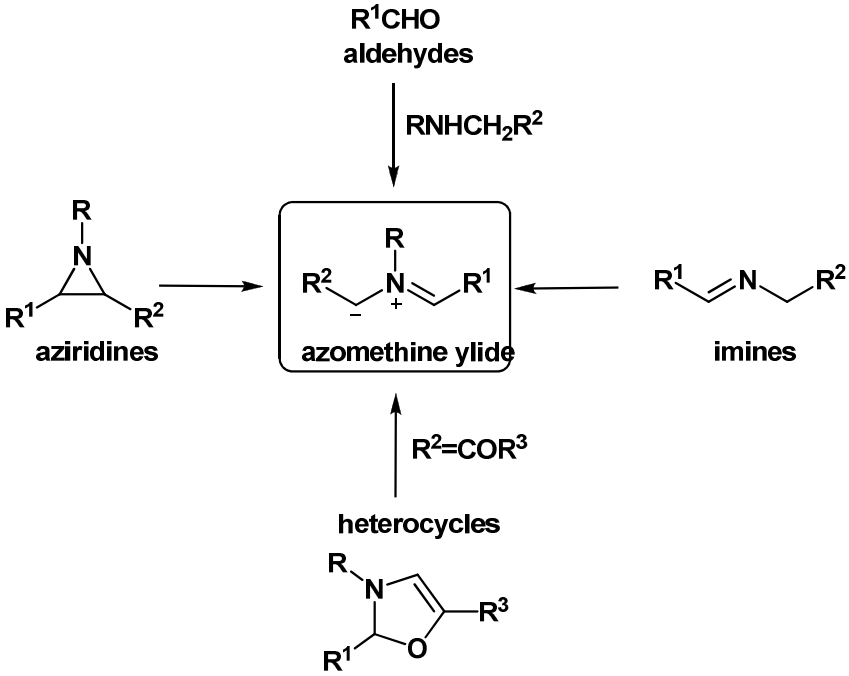
At most, four geometrical isomers are possible for these transient molecules. Their cycloadditions to olefin or acetylene dipolarophiles give rise to the formation of two sets of carbon-carbon bonds in a single step. Because of the structural complexity of azomethine ylide itself compared to other dipoles and the stereochemical selectivity in the cycloadditions, a number of stereoisomers are possible for the cycloadducts. These two points make azomethine ylides one of the most attractive 1,3-dipoles, both in the fields of ylide chemistry and synthetic organic chemistry.



Scheme 1. 8 Stereochemical examination of reaction between (W-U-S) shaped ylide and dipolarophile.

The 1, 3–dipolar cycloaddition of azomethine ylides with alkene or alkyne is a very effective method for the construction of pyrrolidine- and pyrrole-rings in the synthesis of pyrrolidine- and pyrrole-containing molecules. These molecules are very important pharmaceuticals, natural alkaloids, organic catalysts, and building blocks in organic synthesis [46]. As with other cycloaddition reactions, it is generally accepted that the 1,3–dipolar cycloaddition of azomethine ylides follows a concerted pathway and proceeds according to the Woodward-Hoffman rules. However, a stepwise pathway can not be ruled out [47].

Many methods for the formation of azomethine ylides have been developed [48], of which the most common is the reaction of an amine with an aldehyde to form an iminium, followed by the generation of a carboanion. The in situ prepared azomethine ylides are subject instantly to the cycloadditon reaction because they are very labile. Other common methods include the thermal ring-opening of aziridines [49], or heterocyclic compounds such as 4-oxazolines [50] and pyridines [51].



Scheme 1. 9 Different route of synthesis of azomethine ylide

Up to four new chiral centers can be generated in the 1,3-dipolar cycloaddition reaction of azomethine ylides which results from the different ylide geometries, endo/exo selectivity and enantioselectivity. Hence, it is demanding to control the stereochemistry of the 1,3-dipolar cycloaddition reaction of azomethine ylides, to synthesize enantiomerically enriched molecules.

The asymmetric versions of 1,3-DC reactions can be obtained generally in three ways;

* by attaching a chiral auxiliary to the dipole,

* by attaching a chiral auxiliary to the dipolarophile, or

* by employing a chiral Lewis acid (LA) capable of complexing with both 1,3-dipole and dipolarophile [46].

1.5. 8-HYDROXYQUINOLINE

1.5.1. The Properties and Biological Importance of 8-Hydroxyquinoline

8-Hydroxyquinoline is a white to off-white crystalline powder which is obtained from coal tar, but commercially it is prepared by Skraup synthesis using acetic acid instead of sulfuric acid yielding more than 90% of 8-Hydroxyquinoline [52,53].

8-Hydroxyquinoline or 8-quinolinol is the name most frequently used in the analytical literature; the trivial name oxine is very convenient, particularly for the description of the chelate compounds, which may be called oxinates. Of the seven possible quinolinols only 8-quinolinol forms chelate compounds with metal ions.

8-Hydroxyquinoline has a wide variety of uses and its medicinal and agricultural significances were discovered before the start of current century [54,55]. Quinoline family compounds are widely used as a parent compound to make drugs, fungicides, biocidal. 8-Hydroxyquinoline and its derivatives are used due to their biological activity as antibacterial [56], antimalarial [57], antipneumococcic [58], fungicidal [59], antiseptic [60], antituberculotic [61], antineoplastic [62], amebacidal [63], pesticidal [64], anthelmintic [65], and anthidiuretic activities [66]. These properties are closely related with their capability for quelating metallic ions. Existence of hydrogen bonding intra- and intermolecular interaction type O-H, N and their different forces, give these compounds characteristic forms, adopting ring structures of quelating type and dimer forms.

8-Hydroxyquinoline is a metal chelator with antimicrobial and antifungal activity which exists as a free lipophilic base or in form of water soluble salts (e.g. as sulphate).

This MRL application is limited to the use of 8-hydroxyquinoline sulphate for topical treatment of umbilical infections in new born animals (cattle, sheep, goats, pigs and horses). The substance is used at a concentration of 0.1% in an ointment preparation which is also used in human medicine as skin disinfectant and in hair-shampoos at low concentrations of 0.03 to 0.3%. 8- Hydroxyquinoline is very effective as a pesticide for grapevine graft disinfection. 8-Hydroxyquinoline is also used in nuclear medicine and as a preservative for cosmetics, tobacco and wood [67]. 8-Hydroxyquinoline is also used as a precipitating reagent for uranium and other radioactive metals in nuclear power plant liquid waste effluent. More recently, it has been used in extraction of radioactive trivalent lanthanides, polonium and gadolinium from nitrate aqueous medium [68]. 8-Hydroxyquinoline has been found to be non-carcinogenic, employing four commonly used in vitro assays for genetic toxicity [69,70], while recent investigation showed that collagenase inhibitors, useful for inhibition of tumor melastasis and for treatment of rheumatoid arthritis contain 8-hydroxyquinoline or its derivatives.

1.5.2. The Reactions and Preparation of 8-Hydroxyquinoline

Of the seven possible quinolinols only 8-quinolinol forms chelate compounds with metal ions. In addition to chelation reactions 8-quinolinol forms salts with both acids and bases and undergoes most of the typical phenol and quinoline reactions.

In its phenolic properties it resembles α-naphtol except for some decrease in activity and alteration of products in a few reactions, a difference which is due to its chelating and basic functions [71].

8-Hydroxyquinoline shows keto-enol tautomerism. Although 8-quinolinol is said to be in the form of a keto tautomer to an extent of about 30 percent in some solvents [72], the oxinates are not obtained from the keto form [73] but are formed through an electrovalent bond to oxygen and coordinate bond to nitrogen.

8-Hydroxyquinoline is far more sensitive to oxidation than quinoline. The hydroxyl group of 8-hydroxyquinoline is a strong ortho-para-directing influence so that most substituents are introduced in the 5- or 7-position, with the more active electron-seeking reagents substituting in both positions. Generally 5-position is attacked first. For electrophiles the influence of quinoline nitrogen on substitution is neglicible. Phenolic reactions which require catalyst such as zinc and aluminium chlorides as metallic catalyst are much difficult. For example, the Pechmann and Fries reactions on 8-Hydroxyquinoline have been reported unsuccesful and the Friedel-Crafts reaction gave rather poor results [53]. In contrast to above examples, Mannich reaction, *O*-alkylation and allylation of 8-Hydroxyquinoline resulted in very high yield of the products [74-76].

Reactions on 8-Hydroxyquinoline include Michael addition [77], chelation with iron and manganese [78], preparation of 8-methoxy-1-methyl carbostyril [79], carbamate ester [80], and organosilyl derivatives [81]. Recently 8-hydroxyquinoline was subjected to a number of reactions for example, formylation [82], reaction with [(bromomethyl) hydroxy per fluoroisopropyl] furan [83], oxidation with hydrogen per oxide in presence of acetic anhydride (reductant), condensation with hydrazine [84], esterification with indoleacetic acid [85] and chelation for heavy metals removal from hydrocarbon oils.

1.6. INDOLIZINES

1.6.1. The Theoretical Background and Biological Importance of Indolizines

Heterocycles form one of the most important and well investigated classes of organic molecules owing to their occurrance in living organisms and a wide range of biological activity. The key role in heterocyclic chemistry belongs to heteroaromatic structures, in particular to five- and six-membered rings and their fused-ring derivatives. It is well known that the difference in chemical behavior between five- and six-membered rings is accounted for by the different aromaticities and different π-excessive or π-deficient characters of their electronic structures, e.g. pyrrole and pyridine [86,87].

Indolizine is the simplest heteroaromatic molecule containing both a π-excessive pyrrole and a π-deficient pyridine ring with only one bridgehead nitrogen, the whole system being isomeric with indole [88,89].

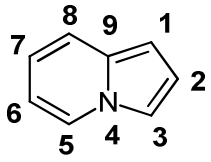


Figure 1. 17 The numbering system for indolizine.

Indolizines are structurally similar to indoles and isoindoles, which are important "molecular templates" for many naturally occuring therapeutics [90-92]. Indolizine derivatives have been repoted to exhibit valuable biological activity against diseases, such as cancer and HIV [93,94]. Indolizine derivatives have also been shown to be antagonistic against neurokinin B (NKB), which is believed to be a major factor in

chronic diseases, such as asthma, in psychiatric disorders and in certain inflammatory diseases [95,96]. In addition, Rise et al. [97] have shown that some indolizine derivatives, especially indolizines with an oxygen atom at C-1 position exhibit activity against lipid peroxidation. Gundersan et al. [98] have reported that indolizine derivatives, oxygenated at C-1, are potent anti-oxidants which inhibit 15-lipoxygenase, an enzyme involved in the oxidation of “low density lipoproteins”, thus leading to the development of atherosclerosis, prostate cancer and spontaneous abortion in animals. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting though mechanisms of action, which are distinct from those of well-known classes of antibacterial agents to which many clinically relevant patogens are now resistant. Majority of tested indolizine compounds showed good antistaphylococcal as well as antimycobacterial activity. The Ames test showed that derivatives of indolizine were investigated for potential mutagenicity and antimutagenic activity [99].The most active indolizine compounds examined carry an α-hydroxybenzyl substituent in the indolizine 1-position which were tested as antimycobacterials against *Mycobacterium tuberculosis* [100]. In pharmaceutical industries, indolizine derivatives are employed as CNS depressant, cardiovascular agents, calcium entry blockers, anti-5-hydroxytryptamine, anti-histamine, anti-acetylcholine, anti-tumor and anticancer agents [101,102]. They are also used in the treatment of angina pectoris. Some of the indolizine derivatives are found to be anti-inflammatory agent. Indolizines are also used as spectral sensitizers, dyes, and intermediates in the synthesis of electron-enriched cycloazines [103,104]. Thus, there is a growing interest in the synthesis of indolizine derivatives. To continue with these important studies, attempts are made to improve the methods of synthesis [105].

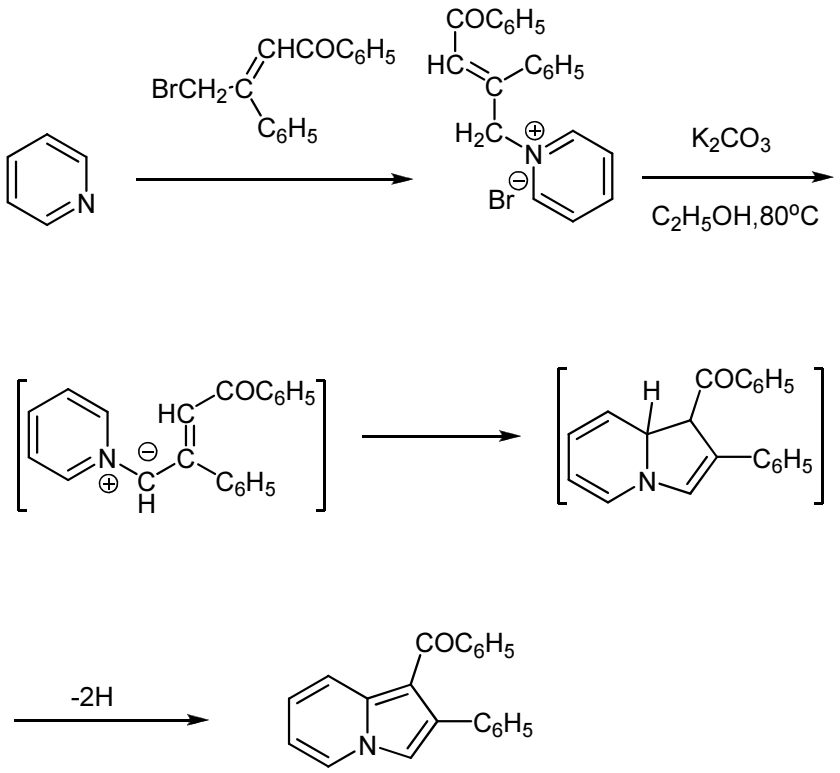
At the present time the chemistry of indolizines constitutes a fairly thoroughly investigated branch of the chemistry of heterocyclic compounds, which was founded by Scholtz and Chichibabin. Scholtz was the first to obtain 1,3-diacetylindolizine from α-picoline and acetic anhydride. He then converted it into indolizine (pyrrocoline) [106-108]. Chichibabin elucidated the mechanism of this reaction [109,110]. He also developed one of the general and most convenient methods for the synthesis of indolizines from 2-methyl-N-β-oxoalkylpyridinium salts [111,112].

Indolizines and their partially or wholly reduced derivatives were comprehensively reviewed in 1948 by Borrows and Holland. They were subsequently mentioned by Elderfield in 1952 and in more detail in 1961 by Mosby covering the literature up to the middle of 1958 [113,114].

1.6.2. The Synthesis of Indolizines from Ylides

Ylides are converted into indolizines either by the cyclisation of the ylides themselves or by their interaction with acetylenic compounds, i.e. via 1,3-dipolar cycloaddition.

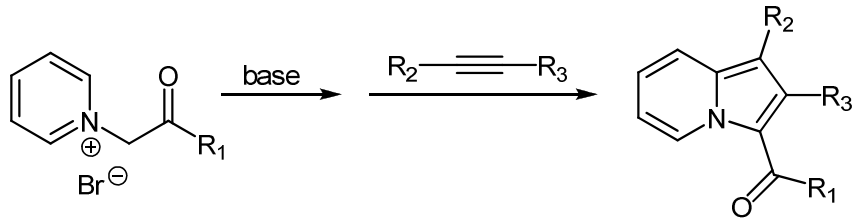
The synthesis of certain substituted indolizines where 4-bromo-1,3-diphenylbut-2-en-1-one was used for the preparation of pyridinium salts have been described. The synthesis of 1-benzoyl-2-phenylindolizine is illustrated in Scheme 1.10 [115].



Scheme 1. 10 The synthesis of indolizine from ylide via cyclisation.

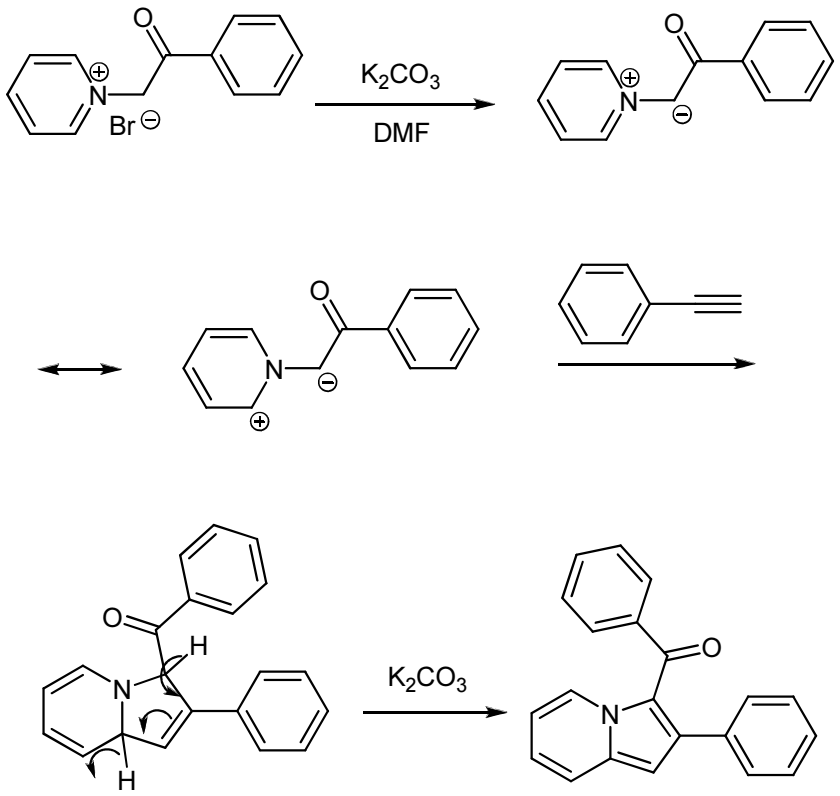
The ylide formed under the conditions of base catalysis cyclises with formation of dihydroindolizine, which is aromatised during the reaction with elimination of hydrogen.

Indolizines can be prepared by the 1,3-dipolar cycloaddition reaction between pyridiniums and carboxylic acid in the presence of a mild base, and many five membered heterocycles can be generated from this method [116,117]. The classic 1,3-dipolar cycloaddition between pyridinium-related heteroaromatic ylides and alkynes is very attractive due to its versatility and efficiency [118,119].



Scheme 1. 11 Synthesis of indolizines from ylides via 1,3-dipolar cycloaddition.

The starting ylide was derived from 1-(2-oxo-2-phenylethyl)pyridinium bromide in the presence of K_2CO_3 in DMF at room temperature. To this mixture was added phenylacetylene, the resulting mixture was heated at 120^{o}C in the sealed flask using the oil bath. After 10h, the major product was formed in 85% yield [120].



Scheme 1. 12 Proposed mechanism of the phenyl(2-phenylindolizin-3-yl)methanone via 1,3-dipolar cycloaddition.

Pyridinium could be deprotonated by K_2CO_3 to give the corresponding ylide, which would act as a dipolar to react with alkyne and generate indolizine via 1,3-dipolar cycloaddition.

1.6.3. The Carbamoyl-substituted Indolizines

The presence of carbamoyl group on the pyrrole ring of the indolizines have interesting effects on their chemical and biological properties. One of the most important methods for the synthesis of indolizines derivatives is based on 1,3-dipolar cycloaddition reactions of N-heterocyclic ylides with electron-deficient alkynes or alkenes [12,121,122].

Carbamoyl-substituted N-bridgehead heterocyclic compounds are obtained by the reactions of N-heterocyclic compounds with chloroacetanilides or bromoacetanilides followed by the direct reactions of the intermediate N-methylcarbamoyl quaternary salts with activated alkynes or alkenes [123].

By the quaternisation reactions of several pyridine, quinoline and isoquinoline derivatives with chloro- or bromoacetanilides the intermediate N-methylcarbamoyl quaternary salts appeared easily accessible.

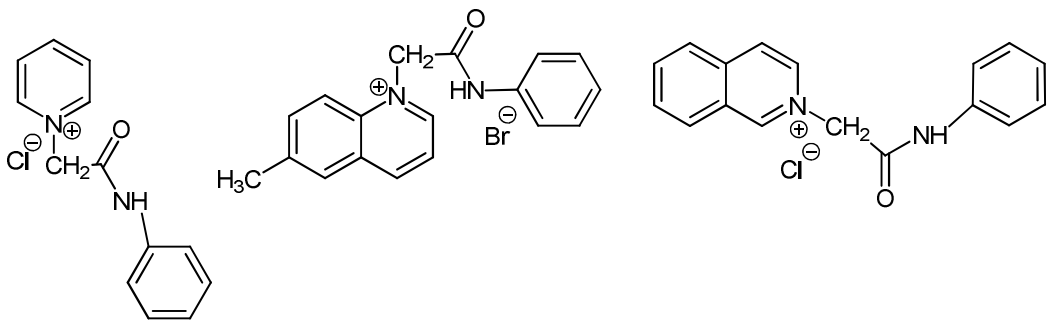
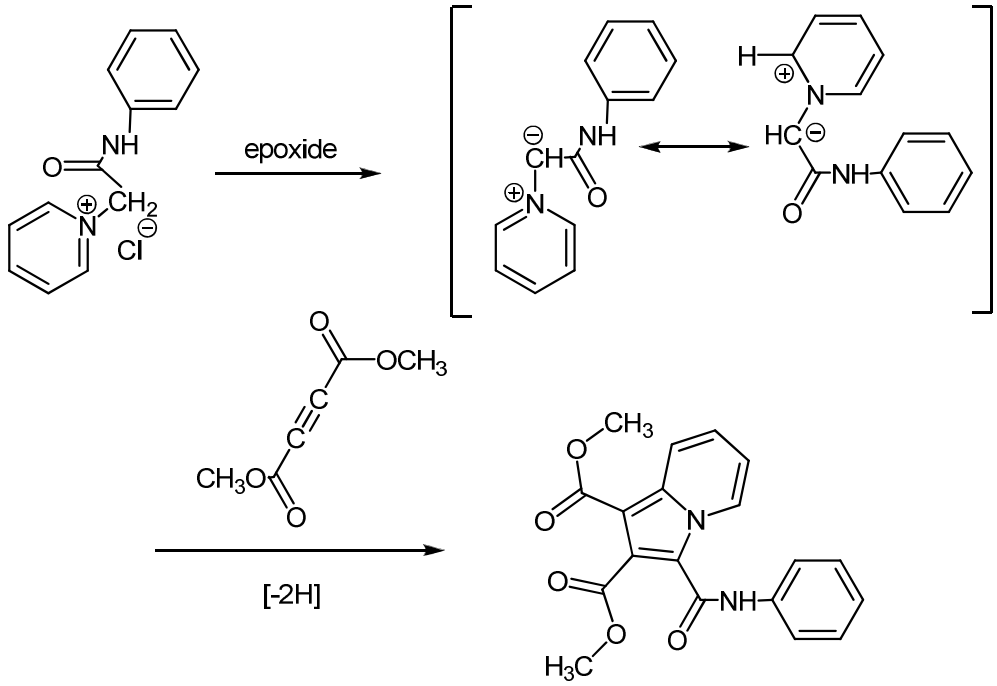


Figure 1. 18 N-Methylcarbamoyl quaternary salts

By the direct reaction of the intermediate N-methylcarbamoyl pyridinium salts with activated alkynes in an epoxide, as acid acceptor and reaction solvent, indolizines bearing a carbamoyl group on the pyrrole ring are obtained [130].



Scheme 1. 13 Synthesis of dimethyl 3-(phenylcarbamoyl)indolizine-1,2-dicarboxylate

1.7. Aim of this work

The aim of this work at the beginning was to study the cycloaddition properties of 8-Hydroxyquinoline derivatives. For this purpose we prepared a lot of quinoline derivatives. But we had some difficulties on their stabilities and reactivities toward cycloaddition reactions. For this reason we changed our target on azomethine ylides.

Hence the aim of this work can be ordered as follows:

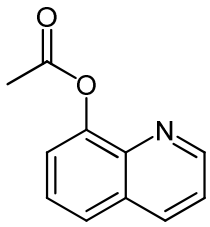
- To synthesize some new carbamoyl substituted indolizines via 1,3-dipolar cycloaddition reactions of azomethine ylides.
- To provide an application of the PMO and FMO methods leading to discussion of the reactivities of the azomethine ylides.
- To make a comprasion the experimental results with the theoretical predictions.
- To introduce new cyclic compounds to the heterocyclic chemistry.

2. EXPERIMENTAL

Melting points were determined with Electrothermal apparatus. IR spectra was recorded on a SHIMADZU FTIR-8400S instruments (Neat or Nujol). ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE spectrometer (400 MHz for proton 100 MHz for carbon). Compounds were purified using preparative thin layer chromatography technique until they were observed as a single spots on thin layer chromatography (Kieselgel HF 254: Ethyl acetate, Dichloromethane, Hexane, Chloroform as eluant)

2.1. Preparation and Rearrangement of 8-Hydroxyquinoline Derivatives

2.1.1. Preparation of 8-acetoxyquinoline (2a) and rearrangement of 8-acetoxyquinoline to 1-acetylquinolinium-8-olate (2b)



(2a)

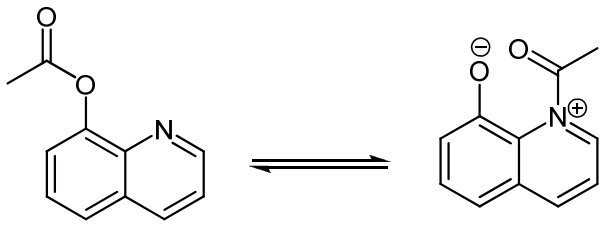
8-Hyroxyquinoline **1a** (2.00 g, 0.0138 mol) in pyridine **1b** (2.00 mL, 0.0253 mol), acetic anhydride **1c** (2.00 mL, 0.0196 mol) were added and the reaction mixture was kept at room temperature 2 hours to give the product of 8-acetoxyquinoline.

This reaction mixture was poured into water and shaken with ethyl acetate and ethyl acetate was removed under vacuum and the liquid condensed phase was obtained. The yield was 59 % (1.677 g).

Color : Orange

IR (Nujol): ν (cm^{-1}) : 1763, 1712, 1597

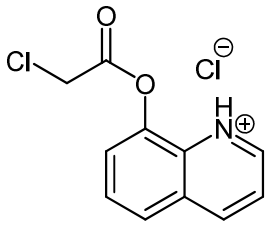
8-acetoxyquinoline rearranged to 1-acetylquinolinium-8-olate after two months.



(2a) **(2b)**

IR (Nujol): ν (cm^{-1}) : 1755, 1707, 1597

2.1.2. Preparation of 8-(2-chloroacetoxy)quinolinium chloride (2c) and rearrangement of 8-(2-chloroacetoxy)quinolinium chloride (2c) to 1-(2-chloroacetyl)-8-hydroxyquinolinium chloride (2d)



(2c)

8-Hydroxyquinoline **1a** (1.00 g, 0.00688 mol) was dissolved in 10 mL of dry THF and chloroacetyl chloride **1d** (0.55ml, 0.00688mol)was added, 5.00 mL of dry THF

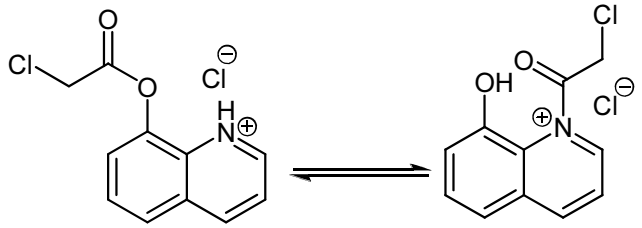
added more and filtered off using THF as a solvent and dried in vacuum desicator, the product was obtained as a yellow color at higher yield of 98 % (1.730 g).

Color : Yellow

M.p. : 134-135^{o}C

IR (Nujol): ν (cm^{-1}) : 3165, 1786, 1649

8-(2-chloroacetoxy)quinolinium chloride **2c** rearranged to 1-(2-chloroacetyl)-8-hydroxyquinolinium chloride **2d** after 1 week.



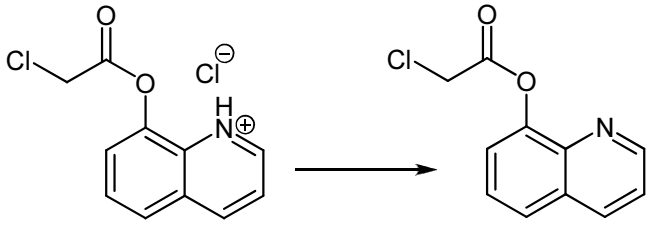
(2c) **(2d)**

After rearrangement ;

M.p. : 208-210 ^{o}C

IR (Nujol): ν (cm^{-1}) : 3331, 1720, 1631

2.1.3. Neutralization of 8-(2-chloroacetoxy)quinolinium chloride (2c) using Et_3N and rearrangement of quinolin-8-yl-2-chloroacetate (2e) to 1-(2-chloroacetyl)quinolinium-8-olate (2f)



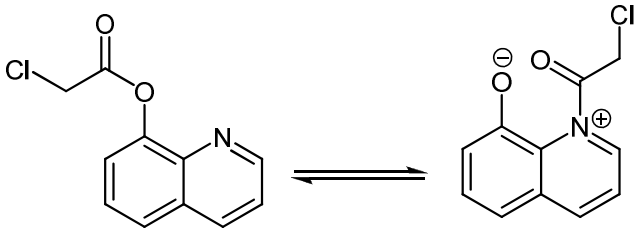
(2c) **(2e)**

8-(2-chloroacetoxy)quinolinium chloride **2c** (0.100 g, 0.387 mmol) was dissolved in 2 mL of THF and added Et_3N (0.036 g, 0.359 mmol, 0.050 mL). The liquid phase was taken using a piece of cotton and the solvent was removed under vacuum. Quinolin-8-yl-2-chloroacetate **2e** was obtained at lower yield in liquid form. The yield was 35 % (0.030g).

Color : Yellow to green

IR (Nujol): ν (cm^{-1}) : 1782, 1629, 1597

Quinolin-8-yl-2-chloroacetate **(2e)** rearranged to 1-(2-chloroacetyl)quinolinium-8-olate **(2f)** after one day.



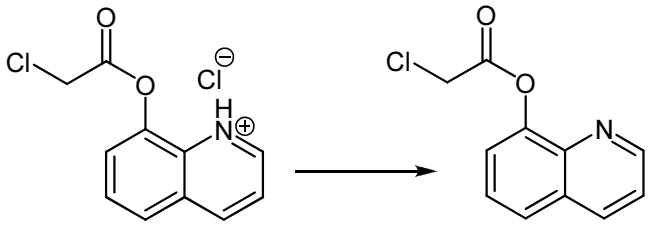
(2e) **(2f)**

1-(2-chloroacetyl)quinolinium-8-olate **2f** was obtained as yellow powders.

M.p. : 96-97 ^{o}C

IR (Nujol): ν (cm^{-1}) : 1643, 1597

2.1.4. Neutralization of 8-(2-chloroacetoxy)quinolinium chloride (2c) using Sodium bicarbonate and rearrangement of quinolin-8-yl-2-chloroacetate (2e) to 1-(2-chloroacetyl)quinolinium-8-olate (2f)



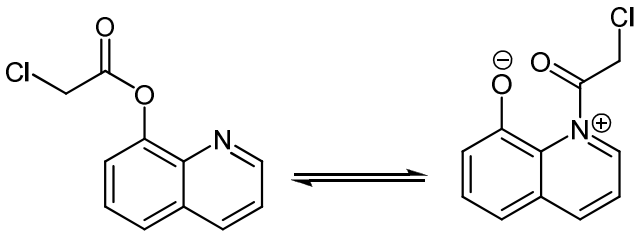
(2c) **(2e)**

Concentrated sodium bicarbonate solution was added slowly to the 8-(2-chloroacetoxy)quinolinium chloride **2c** (0.100 g, 0.387 mmol) and after neutralization it was extracted with ethyl acetate. Quinolin-8-yl-2-chloroacetate **2e** was obtained at higher yield as 85 % (0.073 g).

Color : Yellow to green

IR (Nujol): ν (cm^{-1}) : 1782, 1629, 1597

Quinolin-8-yl-2-chloroacetate **(2e)** rearranged to 1-(2-chloroacetyl)quinolinium-8-olate **(2f)** after one day.



(2e) **(2f)**

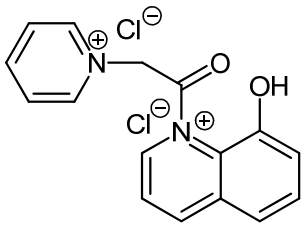
1-(2-chloroacetyl)quinolinium-8-olate **2f** was obtained as yellow powder.

M.p. : 96-97 ^{o}C

IR (Nujol): ν (cm^{-1}) : 1643, 1597

2.1.5. Preparation of 8-hydroxy-1-(2-(pyridinium-1-yl)acetyl)quinolinium chloride (2h) and 1-(2-(pyridinium-1-yl)acetyl)quinolinium-8-olate chloride (2k)

2.1.5.1. Preparation of 8-hydroxy-1-(2-(pyridinium-1-yl)acetyl)quinolinium chloride (2h)



(2h)

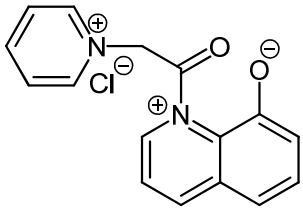
1-(2-chloroacetyl)-8-hydroxyquinolinium chloride **2d** (0.100 g, 0.387 mmol) was added to pyridine **1b** (0.059 g, 0.774 mmol, 0.060 mL) and the mixture was kept at room temperature for 2 days to give the product 8-hydroxy-1-(2-(pyridinium-1-yl)acetyl)quinolinium chloride **2h** which was washed with dichloromethane. The yield was 88 % (0.115 g).

Color : Dark yellow

M.p. : 183-184 ^{o}C

IR (Nujol): ν (cm^{-1}) : 3427, 1724

2.1.5.2. Preparation of 1-(2-(pyridinium-1-yl)acetyl)quinolinium-8-olate chloride (2k)



(2k)

1-(2-chloroacetyl)quinolinium-8-olate **2f** (1.350 g, 6.090 mmol) was added to pyridine **1b** (0.589 g, 7.450 mmol, 0.600 mL) and the mixture was kept at room temperature for 2 days to gave the product 1-(2-(pyridinium-1-yl)acetyl)quinolinium-8-olate chloride **2k** which was washed with dichloromethane. The yield was 71 % (1.300 g).

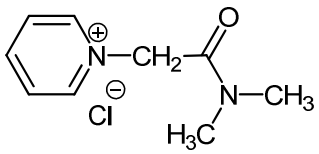
Color : Light yellow

M.p. : 134-135 ^{o}C

IR (Nujol): ν (cm^{-1}) : 3392, 1724

2.2. Synthesis of starting compounds of azomethine ylides and their cycloadducts

2.2.1. Synthesis of unsubstituted pyridinium chloride (3a)



(3a)

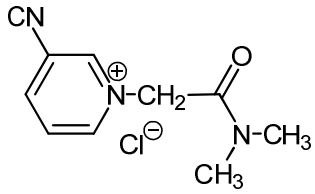
2-Chloro-N,N-dimethylacetamide **1e** (1.510 g, 0.012 mol, 1.300 mL) was added to pyridine **1b** (0.982 g, 0.012 mol, 1.000 mL) and the mixture was kept at 20 ºC for 3 h. The mixture pyridinium chloride **3a** was obtained. The precipitate was washed with diethyl ether. The yield was 98 % (2.440 g).

M.p. : 82-84 ºC

Color : White

IR (Nujol): ν (cm^{-1}) : 1658, 1639, 1585

2.2.2. Synthesis of 3-cyanopyridinium chloride (3b)

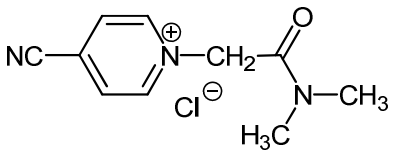


(3b)

2-Chloro-N,N-dimethylacetamide **1e** (1.167 g, 0.009 mol, 1.000 mL) was added to 3-cyanopyridine **1f** (1.000 g, 0.009 mol, 0.086 mL) and the mixture was kept at 20 ºC for 1 week. The precipitated 3-cyanopyridinium chloride **3b** was filtered off. The precipitate was washed with diethyl ether. The yield was 55 % (1.200 g).

M.p.	:77-79 ºC
Color	: Light yellow to light pink
IR (Nujol): ν (cm^{-1})	: 2251, 1662, 1635, 1581

2.2.3. Synthesis of 4-cyanopyridinium chloride (3c)



(3c)

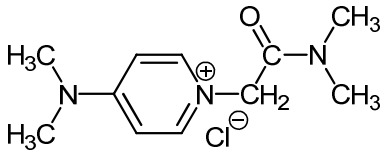
2-Chloro-N,N-dimethylacetamide **1e** (1.477 g, 0.012 mol, 1.250 mL) was added to 4-cyanopyridine **1g** (1.000 g, 0.009 mol, 0.086 mL) and the mixture was kept at 20 ºC for 3 days. The precipitated 4-cyanopyridinium chloride **3c** was filtered off. The precipitate was washed with diethyl ether. The yield was 40 % (0.800g).

M.p. : 212-213 ºC

Color : White to light pink

IR (Nujol): ν (cm^{-1}) : 1654, 1647, 1566

2.2.4. Synthesis of 4-dimethylaminopyridinium chloride (3d)



(3d)

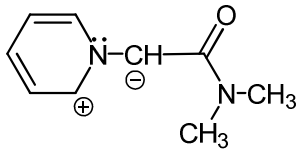
2-Chloro-N,N-dimethylacetamide **1e** (0.497 g, 0.0041 mol, 0.420 mL) was added to 4-Dimethylaminopyridine **1h** (0.500 g, 0.0041 mol) and the mixture was kept at 20 ºC for 1 day. The precipitated 4-dimethylaminopyridinium chloride **3d** was filtered off. The precipitate was washed with diethyl ether. The yield was 82 % (0.815 g).

M.p. : 262-264 ºC

Color : White to light green

IR (Nujol): ν (cm^{-1}) : 1654, 1560, 1498

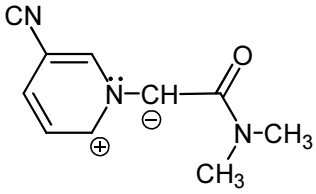
2.2.5. Synthesis of unsubstituted pyridinium ylide (4a)



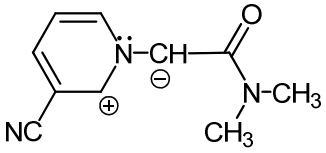
(4a)

Azomethine ylide **4a** was prepared in situ by adding (0.252 g, 0.0025 mol, 0.350 mL) triethylamine to pyridinium chloride **3a** (0.500 g, 0.0025 mol) in 5 mL $CHCl_3$.

2.2.6. Synthesis of 3-cyanopyridinium ylide (4b) or (4b')



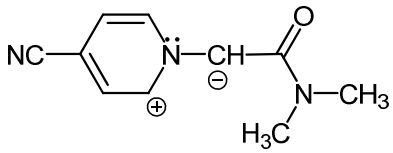
(4b)



(4b')

Azomethine ylide **4b, 4b'** was prepared in situ by adding (0.224 g, 0.0022 mol, 0.300mL) triethylamine to 3-cyanopyridinium chloride **3b** (0.500 g, 0.0022 mol) in 10 mL $CHCl_3$.

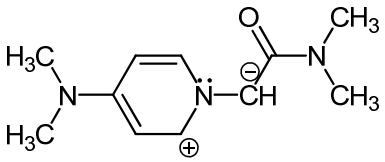
2.2.7. Synthesis of 4-cyanopyridinium ylide (4c)



(4c)

Azomethine ylide **4c** was prepared in situ by adding (0.224 g, 0.0022 mol, 0.300 mL) triethylamine to 4-cyanopyridinium chloride **3c** (0.500 g, 0.0022 mol) in 10 mL $CHCl_3$.

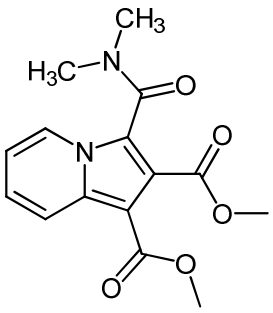
2.2.8. Synthesis of 4-dimethylaminopyridinium ylide (4d)



(4d)

Azomethine ylide **4d** was prepared in situ by adding (0.207 g, 0.0021 mol, 0.286 mL) triethylamine to 4-dimethylaminopyridinium chloride **3d** (0.500 g, 0.0021 mol) in 10 mL $CHCl_3$.

2.2.9. Reaction of unsubstituted pyridinium ylide with dimethyl acetylenedicarboxylate (DMAD)



(5a)

Dimethyl acetylenedicarboxylate (0.405 g, 0.0029 mol, 0.350 mL) was added to azomethine ylide **4a** (prepared by using 0.500 g **3a** and 0.350 mL triethylamine in 5 mL $CHCl_3$) and the mixture was stirred 1 day at room temperature. The solvent was removed under vacuum and the product dimethyl 3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5a** was separated by preparative t.l.c. (silica gel; Dichloromethane-Ethyl acetate 9:1). Elution with ethyl acetate gave a light blue liquid product (52%, 0,400g).

M.p. : Not specified (Product was oily)

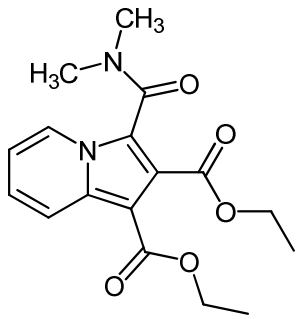
R_f : 0.35 (EtOAc)

IR (Neat): ν (cm^{-1}) : 1732, 1701, 1627

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.13-8.09 (2d, *J* =7.2, 9.2 Hz, 2H), 7.10-7.06 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.77-6.74 (t, *J* = 1.2, 6.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.00 (s, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 164.1, 162.7, 161.0, 135.0, 124.6, 123.2, 120.9, 119.2, 113.1, 101.3, 95.1, 51.4, 50.4, 35.8

2.2.10. Reaction of unsubstituted pyridinium ylide with diethyl acetylenedicarboxylate (DEAD)



(5b)

Diethyl acetylenedicarboxylate (0.480 g, 0.0028 mol, 0.450 mL) was added to azomethine ylide **4a** (prepared by using 0.500 g **3a** and 0.350 mL triethylamine in 5 mL $CHCl_3$) and the mixture was stirred 1 day at room temperature. The solvent was removed under vacuum ant the product diethyl 3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5b** was seperated by preparative thin layer chromatography (silica gel; Ethyl acetate). Elution with ethyl acetate gave a liquid light yellow to green product (44%, 0.360g).

M.p. : Not specified (Product was oily)

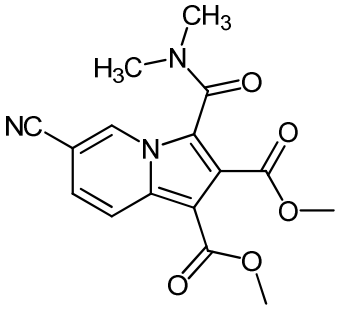
R_f : 0.35 (Ethyl acetate)

IR (Neat): ν (cm^{-1}) : 1735, 1701, 1635

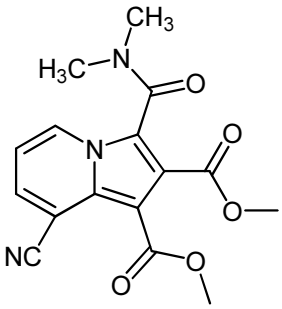
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.13-8.11 (d, *J* = 8.8 Hz, 2H), 7.1-7.06 (dd, *J* = 6.8, 9.6 Hz, 1H), 6.77-6.73 (t, *J* = 1.2, 6.8 Hz, 1H), 4.32-4.26 (m, 4H), 3.00 (s, 6H), 1.33-1.27 (m, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 163.6, 162.4, 161.2, 134.9, 124.6, 123.1, 121.3, 119.2, 113.0, 101.6, 95.1, 60.3, 59.0, 35.9, 13.4, 13.1

2.2.11. Reaction of 3-cyanopyridinium ylide with dimethyl acetylenedicarboxylate (DMAD)



(5c)



(5c')

Dimethyl acetylenedicarboxylate (0.440 g, 0.0031 mol, 0.380 mL) was added to azomethine ylide **4b** (prepared by using 0.700 g **3b** and 0.430 mL triethylamine in 10 mL $CHCl_3$) and the mixture was stirred 2 days at room temperature. The solvent was removed under vacuum and the product dimethyl 6-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5c** was seperated by preparative thin layer chromatography (silica gel; Ethyl acetate-Hexane 2:1). Elution with ethyl acetate gave a yellow product (10%, 0.070g).

M.p. : Not specified (Product was oily)

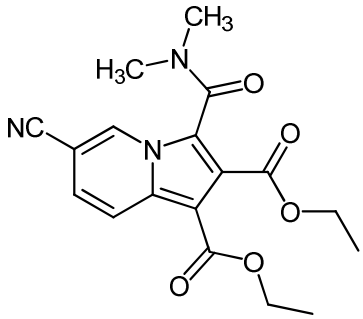
R_f : 0.72 (EtOAc)

IR (Neat): ν (cm^{-1}) : 2235, 1728, 1703, 1633

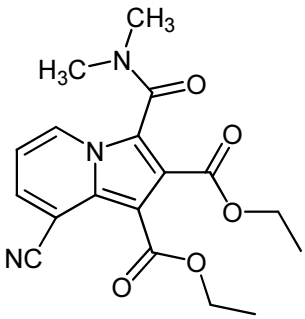
^1H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.66 (s, 1H), 8.21-8.18 (d, *J* = 9.6 Hz, 1H), 7.16-7.13 (dd, *J* = 1.4, 9.2 Hz 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.03 (s, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 163.1, 161.8, 159.8, 133.9, 131.3, 122.7, 122.2, 120.2, 114.8, 103.9, 99.6, 95.1, 51.7, 50.7, 36.0

2.2.12. Reaction of 3-cyanopyridinium ylide with diethyl acetylenedicarboxylate (DEAD)



(5d)



(5d')

Diethyl acetylenedicarboxylate (0.376 g, 0.0022 mol, 0.350 mL) was added to azomethine ylide **4b** (prepared by using 0.500 g **3b** and 0.300 mL triethylamine in 10 mL $CHCl_3$) and the mixture was stirred 4 days at room temperature. The solvent was removed under vacuum and the product diethyl 6-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5d** was seperated by preparative thin layer chromatography (silica gel; Dichloromethane-Ethyl acetate 9:1). Elution with ethyl acetate gave a yellow product (16%, 0.124).

M.p. : Not specified (Product was oily)

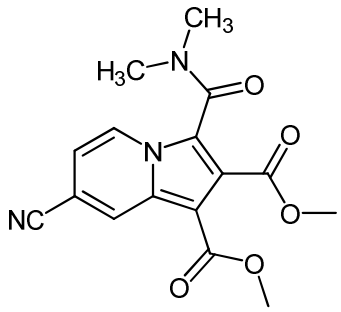
R_f : 0.72 (EtOAc)

IR (Neat): ν (cm^{-1}) : 2233, 1735, 1701, 1639

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.65 (s, 1H), 8.22-8.19 (dd, *J* = 1.2, 10.4 Hz, 1H), 7.15-7.12 (dd, *J* = 1.4, 10.8 Hz, 1H), 4.34-4.28 (m, 4H), 3.03 (s, 6H), 1.34-1.28 (m, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 162.4, 161.2, 159.7, 133.6, 130.9, 122.7, 121.7, 119.9, 118.5, 114.6, 103.9, 94.8, 60.5, 59.3, 35.8, 13.0, 12.8

2.2.13. Reaction of 4-cyanopyridinium ylide with dimethyl acetylenedicarboxylate (DMAD)



(5e)

Dimethyl acetylenedicarboxylate (0.319 g, 0.0022 mol, 0.270 mL) was added to azomethine ylide **4c** (prepared by using 0.500 g **3c** and 0.300 mL triethylamine in 10 mL $CHCl_3$) and the mixture was stirred 1 day at room temperature. The solvent was removed under vacuum and the product dimethyl 7-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5e** was separated by preparative thin layer chromatography (silica gel; Dichloromethane-Ethyl acetate 9:1). Elution with ethyl acetate gave a brown product (39%, 0.280g) as neddles.

M.p. : 178-180 ºC

R_f : 0.42 (Dichloromethane-Ethyl acetate 9:1)

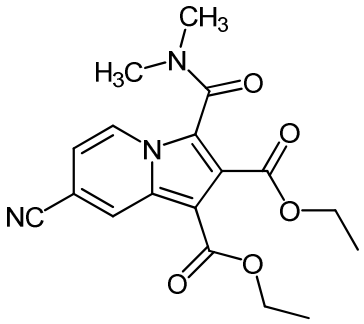
IR (Nujol): ν (cm^{-1}) : 2220, 1735, 1720, 1635

Elemental Analysis : 58.98 % C, 4.79 % H, 12.43 % N (Theoretical value: 58.36 % C, 4.59 % H, 12.76 % N)

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.52 (s, 1H), 8.20-8.18 (d, *J* = 7.6 Hz, 1H), 6.87-6.85 (dd, *J* = 1.8, 7.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.01 (s, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 163.0, 161.6, 159.8, 149.6, 131.9, 125.6, 122.1, 120.6, 116.1, 112.6, 106.0, 95.0, 51.7, 50.9, 35.9

2.2.14. Reaction of 4-cyanopyridinium ylide with diethyl acetylenedicarboxylate (DEAD)



(5f)

Diethyl acetylenedicarboxylate (0.376 g, 0.0022 mol, 0.350 mL) was added to azomethine ylide **4c** (prepared by using 0.500 g **3c** and 0.300 mL triethylamine in 10 mL $CHCl_3$) and the mixture was stirred 1 day at room temperature. The solvent was removed under vacuum and the product diethyl 7-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate **5f** was separated by preparative thin layer chromatography (silica gel; Dichloromethane-Ethyl acetate 9:1). Elution with Ethyl acetate gave a light blue liquid product (28%, 0.224g).

M.p. : Not specified (Product was oily)

R_f : 0.42 (Dichloromethane-Ethyl acetate 9:1)

IR (Neat): ν (cm^{-1}) : 2227, 1728, 1705, 1635

^1H NMR (δ_H, 400 MHz, $CDCl_3$) : 8.51 (s, 1H), 8.18-8.16 (dd, *J* = 1.2, 7.2 Hz, 1H), 6.86-6.83 (dd, *J* = 1.8, 7.6 Hz, 1H), 4.35-4.28 (m, 4H), 3.00 (s, 1H), 1.35-1.28 (m, 6H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) : 162.7, 161.6, 160.2, 132.2, 126.2, 125.5, 122.6, 120.8, 116.5, 112.8, 106.1, 95.4, 61.0, 60.0, 40.3, 36.1, 13.5, 13.3

3. RESULT&DISCUSSION

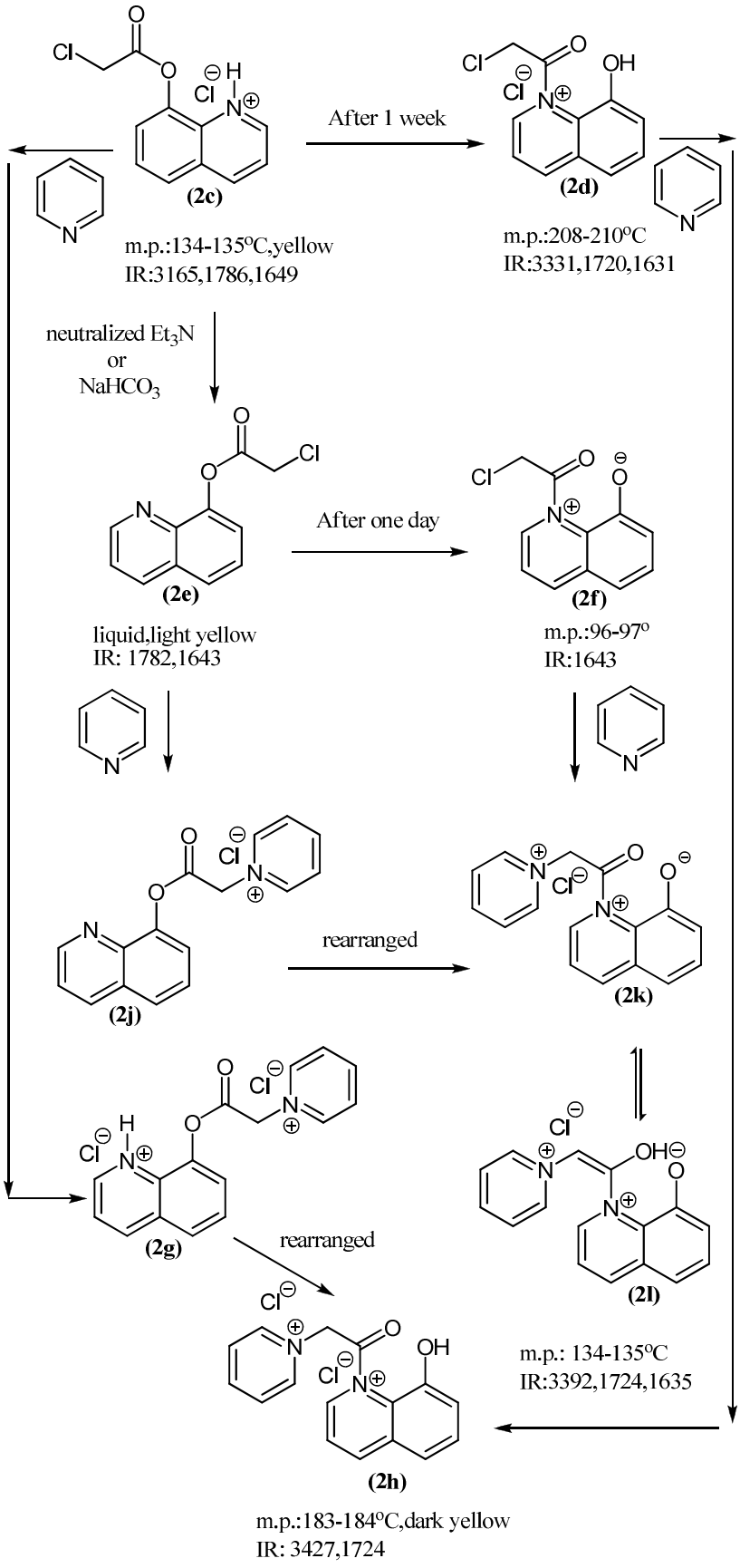
This work covers the investigation of the preparation and rearrangement of 8-hydroxyquinoline derivatives and also the synthesis of new carbamoyl substituted indolizines via 1,3-dipolar cycloaddition reactions of azomethine ylides.

In the first part of the study the preparation and rearrangement of 8-hydroxyquinoline derivatives were studied. 8-Hydroxyquinoline from other quinoline derivatives of the ring nitrogen with the hydroxyl groups in shows through so many concessions because of special relations. This relation brings about lots of reason in our reactions due to the fact that it shows keto-enol tautomerism.

Reaction between 8-hydroxyquinoline **1a** and chloroacetyl chloride **1d** give the product of 8-(2-chloroacetoxy)quinolinium chloride **2c** at higher yield. **2c** rearranged to **2d** after one week. This rearrangement can be understood following the IR spectrum. In **2c** IR spectrum, it is possible to see ester group at 1786 cm^{-1} and its IR spectra supports the structure of **2c** on the other hand in **2d** IR spectrum did not support to **2c** spectra because of the amide groups to be seen instead of ester groups. This peak at 1643 cm^{-1} steer us towards introspection in point of shifting carbonyl group on the nitrogen atom. Hence, it can be thought of IR spectra supports the structure of **2d**. Also, it can be clearly seen absorbtions for hydroxyl groups [ν (nujol) (O-H) 3331 cm^{-1}], amide group [ν (nujol) (C=O) 1631 cm^{-1}]. If pyridine adds directly to the product of **2c**, it will give the product **2g**.

Pyridine is added to the product **2d** in the same way will create product **2h** which is based on differences in melting points and IR spectra might be the **2h** product can be supported. If the product of **2c** is neutralized with triethylamine or sodium bicarbonate, **2e** structure can obtain which is liquid yellow to green color gives an absorbtion at 1782cm^{-1}. It is not seen any N-H peak around 3500-3000 cm^{-1} that can prove the neutralization is succesfully achived in this way, but the product **2e** sojourn only one day in that structure before the rearrangement to the **2f** structure. In this manner the product **2f** can be obtained only waiting one day without doing any procedure. The **2f** structure is supported by the IR absorbtion for amide group [ν (nujol) (C=O) 1643 cm^{-1}] and melting point. The product **2f** is more decisive than **2e** and therefore pyridine added to the **2f** in order to obtain the product **2k** which shows keto-enol tautomerism. It is in a state of equilibrium with **2l** structure. Therefore, cycloaddition reaction was tried with the more stable structure **2k** without using triethylamine as a base for ylide preparation because of to be potential dipole and the dimethyl acetylenedicarboxylate as a dipolaraphile, but the reaction was failed because of not seeing any evident spot in the thin layer spectroscopy following the reaction in the course of two weeks. The cycloaddition reaction was tried with only acetylenic dipolaraphiles such as dimethyl acetylenedicarboxylate because of the fact that they were expected to show great reactivity towards dipoles apart from the other olefinic dipolaraphiles.

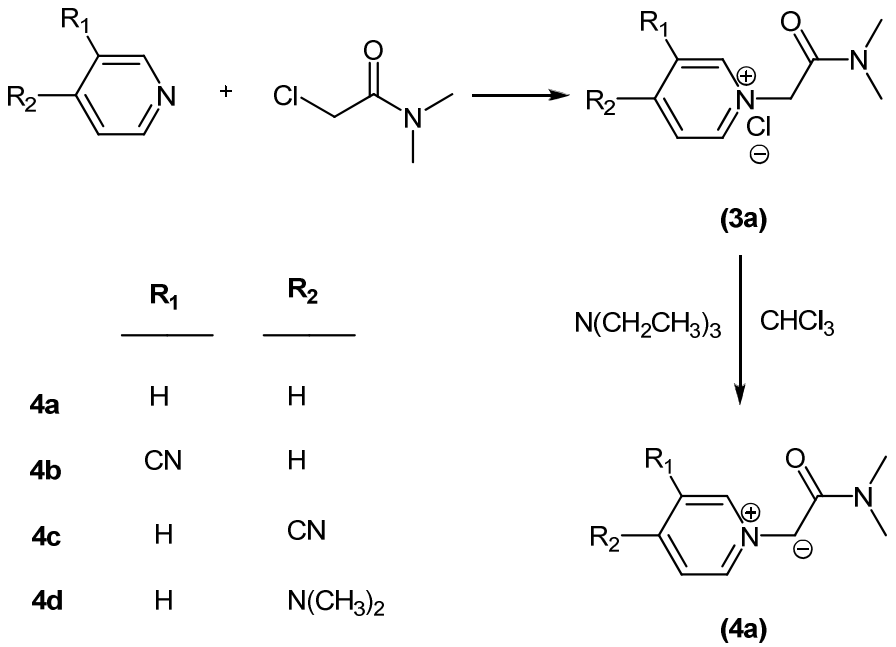
The rearrangements are more clearly seen in the scheme 1.14.



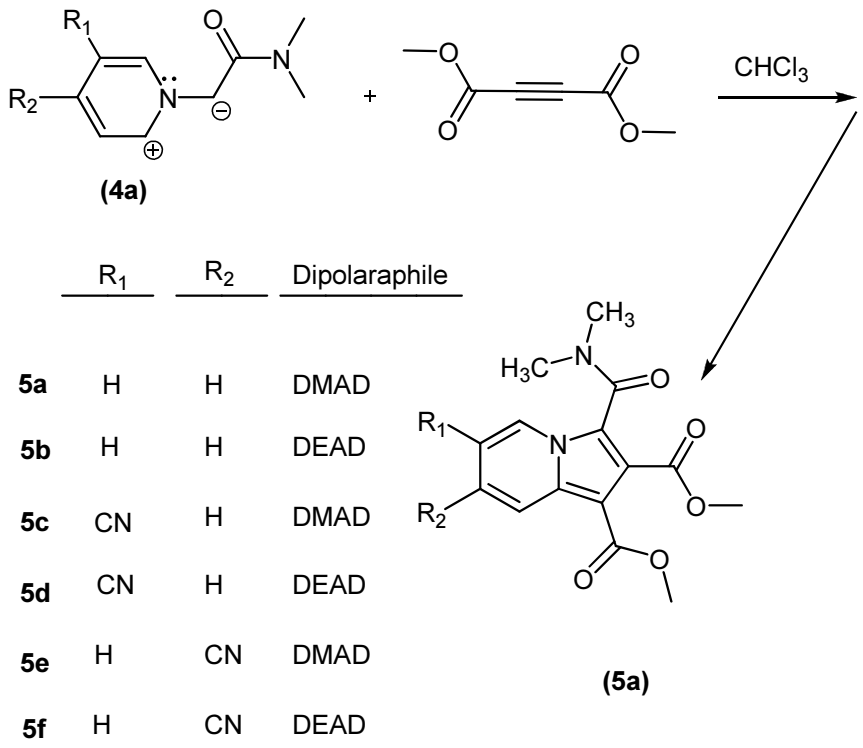
Scheme 1. 14 Rearrangement of the 8-hydroxyquinoline derivatives.

The second part of the study includes synthesis of azomethine ylides and their cycloadducts. The 1,3-dipolar cycloaddition of azomethine ylides has emerged as a popular way of constructing heterocycles owing to its high synthetic efficiency and often high stereoselectivity [124]. Azomethine ylides have traditionally been generated bearing various stabilizing substituents such as aryl groups, esters, and cyano groups. However, the formation of azomethine ylides without such stabilizing groups has proved far more difficult [125].

Pyridine was mixed with 2-chloro-N,N-dimethylacetamide to yield the pyridinium chloride salt **3a**. Removing a proton from methylene group by using triethylamine as a base gave the corresponding unsubstituted azomethine ylide **4a** in $CHCl_3$. Pyridinium ylides such as 3-cyanopyridinium ylide **4b**, 4-cyanopyridinum ylide **4c**, and 4-dimethylaminopyridinium ylide **4d** prepared in the same procedure. (Scheme 1.15)



Scheme 1. 15 The schematic representation of the synthesis of azomethine ylide 4a



	R_1	R_2	Dipolaraphile
5a	H	H	DMAD
5b	H	H	DEAD
5c	CN	H	DMAD
5d	CN	H	DEAD
5e	H	CN	DMAD
5f	H	CN	DEAD

Scheme 1. 16 The schematic representation of the synthesis of cycloadduct 5a

The IR spectrum of **3a**, shows an amide group [ν (nujol) (C=O) 1658 cm^{-1}], an imine stretching band [ν (nujol) (C=N) 1639 cm^{-1}], and an aromatic stretching band [ν (nujol) (C=C) 1585 cm^{-1}]. (Figure 1.19)

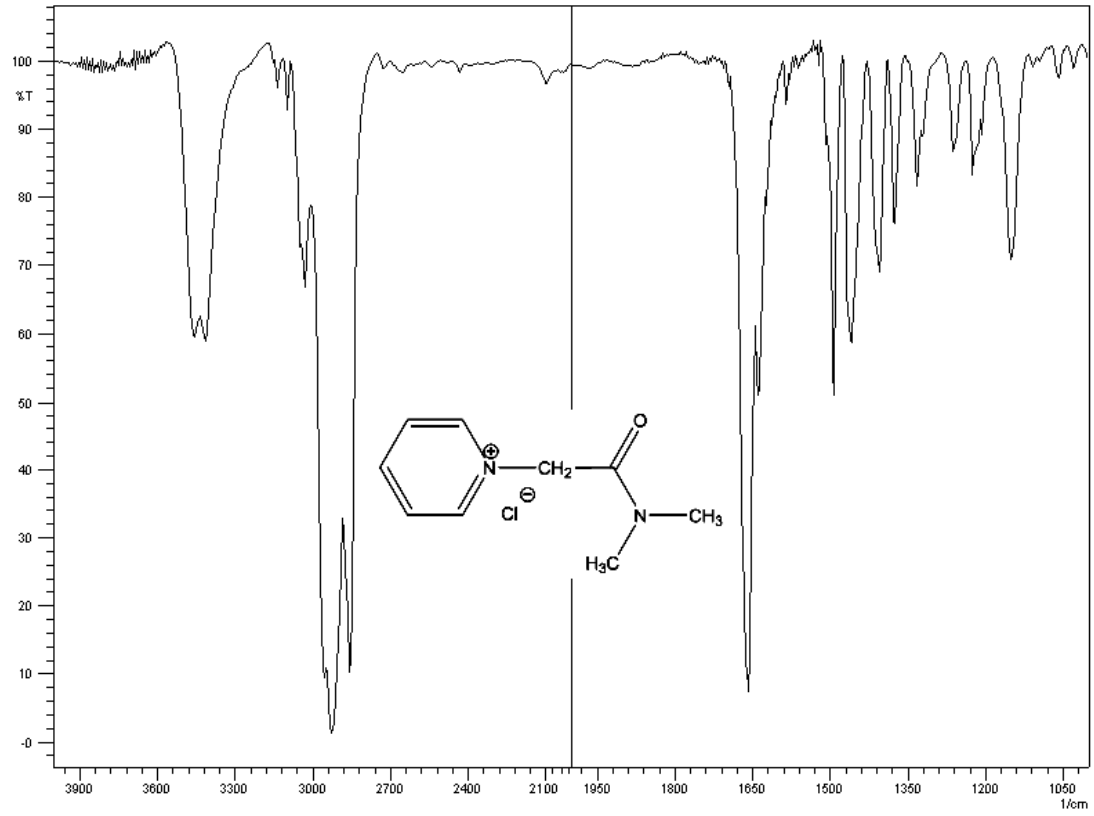


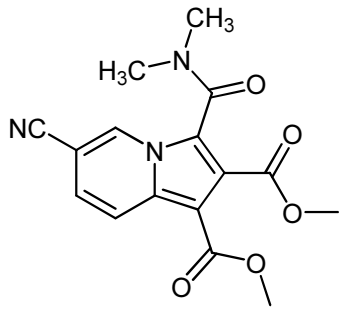
Figure 1. 19 The IR spectrum of unsubstituted pyridinium chloride 3a (In Nujol)

The intermolecular 1,3-dipolar cycloaddition reaction is particularly valuable in indolizine synthesis, being a simple two step process. However, the reaction suffers from low yields and regioselectivity problems when unsymmetrical, highly functionalized or sterically hindered acetylenes are used as substrates [94]. Another drawback is the fact that the pyridinium salt intermediates are highly hygroscopic, and are usually unstable [126].

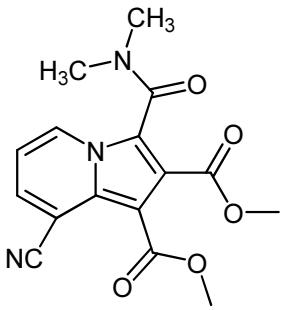
Pyridinium ylides 4a, 4b and 4c were prepared in situ using triethylamine as a base which reacting with acetylenic and olefinic dipolaraphiles in chloroform to produce indolizines. The yields had moderate to low values based on the base and solvent which were used in the reaction conditions.

For the indolizine synthesis the best method of preparation of pyridinium ylides can be using K_2CO_3 as a base instead of Et_3N based on the literature related with indolizine synthesis [120,127]. Attempts were made to improve the yields by conducting the reactions in different bases such as Et_3N, pyridine, NaOH, $NaHCO_3$. However, the yields over than using K_2CO_3 were not observed when the other bases were tried. The same approximation could be made for the solvent. When the solvents are compared with each other, DMF can be more suitable than $CHCl_3$ with the particular consideration of increasing yield.

Acetylenic dipolaraphiles which are dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate were found to be more reactive than olefinic dipolaraphiles such as diphenyl acetylene, phenyl acetylene and vinyl acetate. In this study, dipoles show reactivity with DMAD and DEAD at room temperature in $CHCl_3$ not to necessitate increasing temperature. In view of olefinic dipolaraphiles, these three dipolaraphiles do not show any reactivity towards dipoles whether the temperature increased or not. In this study, four types of pyridinium ylides were prepared from pyridine, 3-cyanopyridine, 4-cyanopyridine and 4-dimethylaminopyridine. Pyridinium ylide and 4-cyanopyridinium ylide are symmetrical. In so far as 3-cyanopyridinium ylide is non-symmetrical, it is expected to get two regioisomer from the reaction, but only one regioisomer can be characterized on account of the fact that the other regioisomer is generated after purification [128].



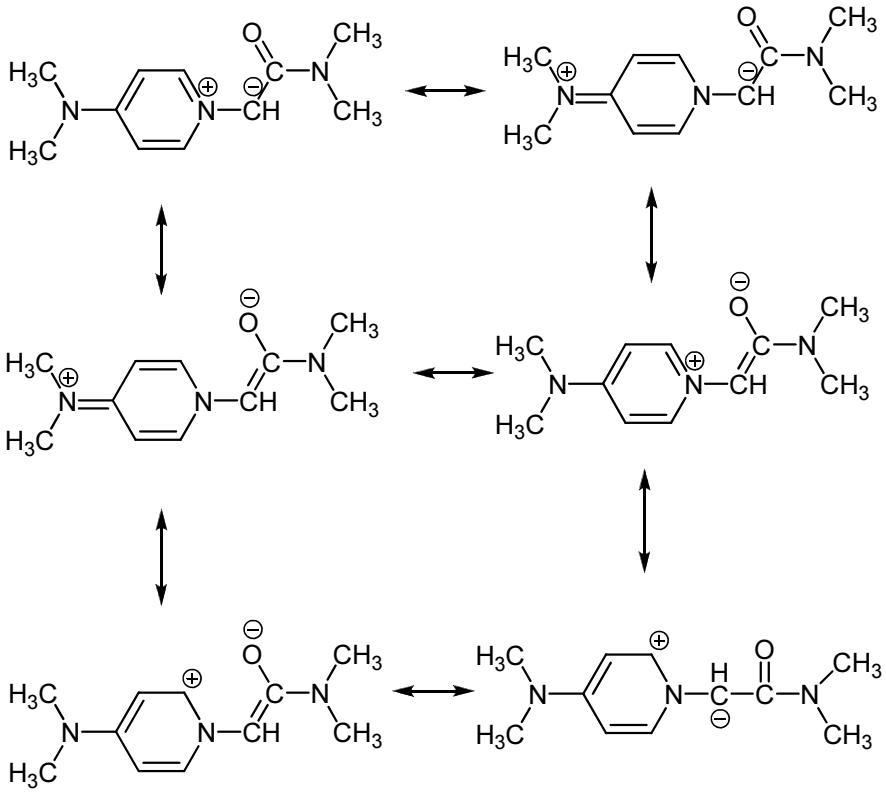
Regioisomer 5c



Regioisomer 5c'

Hence, the other regioisomer **5c'** could not be obtained because of the fact that it was not be stable and silica gel used in preparative thin layer chromatography which behaved as a catalyst forming an obstacle by way of disaggregating the regioisomer into intermediates. Thereby, only one regioisomer **5c** and **5d** could be obtained from the 3-cyanopyridinium ylide in lower yield and the other regioisomer **5c'** and **5d'** could not be obtained for characterization owing to the disaggregation. Try as we might, 2-cyanopyridinium chloride could not be prepared in no way due to the steric hinderance.

4-dimethylaminopyridinium chloride **3d** was prepared in higher yield, but it has the features that attracts moisture like the other pyridinium chloride salts. Its resonance effect is to create a barrier to generate a pyridinium ylide as a dipole for 1,3-dipolar cycloaddition reactions. Therefore, any stable cycloadduct was not obtained reacting with acetylenic dipolarophiles such as dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate which are described as a reactive.



Scheme 1. 17 A representation of 4-dimethylaminopyridinium ylide by resonance structures.

3.1. Characterization of Cycloadducts

3.1.1. Characterization of dimethyl 3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate (5a)

The cycloadduct **5a** is supported by the IR absorbtions for α,β-unsaturated ester groups [ν (neat) (C=O) 1732 and 1701 cm^{-1}] and an amide group [ν (neat) (C=O) 1627 cm^{-1}].(Figure 1.20)

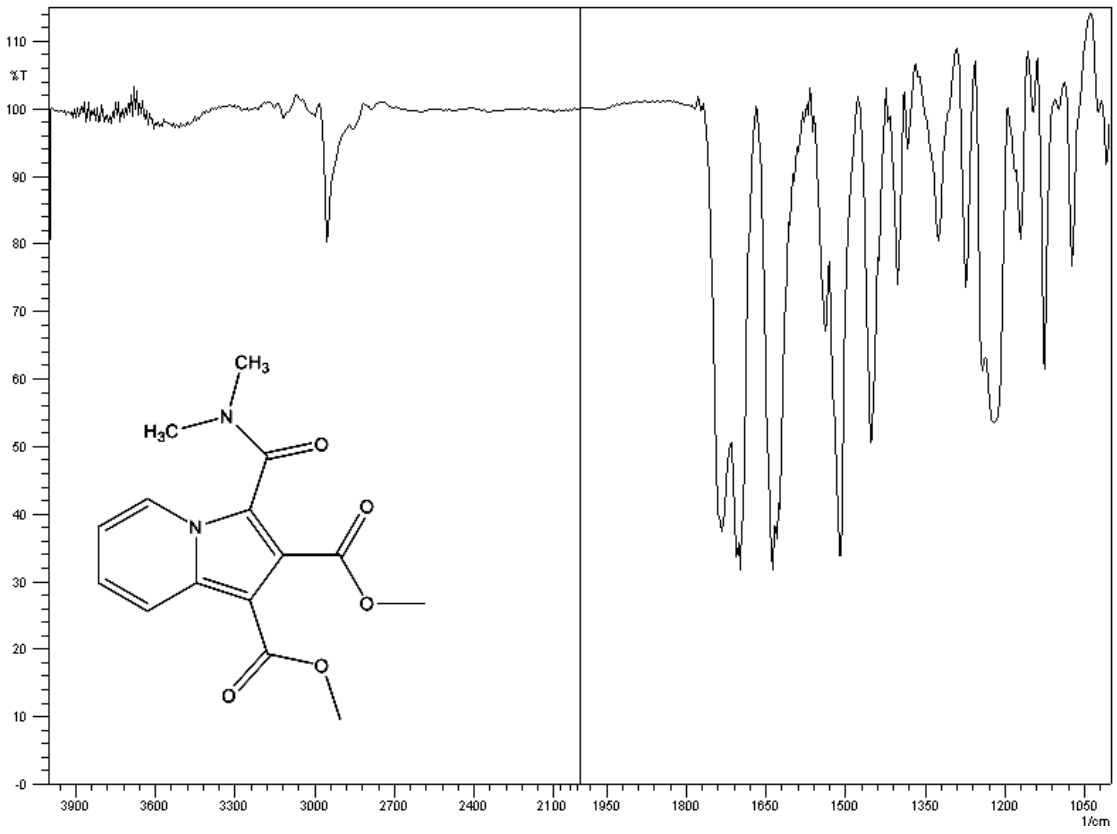


Figure 1. 20 The IR Spectrum of 5a

The ^{1}H NMR spectrum of **5a** shows us structure 5a includes six types of protons and their expansions, coupling constants and their chemical shifts support structure 5a is true. Firstly, the ^{1}H NMR spectrum of 5a shows two doublets which indicates two protons H_a and H_d centered at 8.10 and 8.12 ppm, respectively. H_a couples only with H_b (J_{ab} = 9.2 Hz) and H_d couples only with H_c (J_{dc} = 7.2 Hz). It couldn't be seen long range coupling in the spectrum H_a with H_c or H_d with H_b. In that position, it is possible to say H_d has higher ppm value than H_a in that H_d is near to more electronegative nitrogen atom. Therefore, H_d comes firstly in low field but on the other hand, H_a comes in high field comparad to H_d. H_b makes coupling firstly H_a and H_c which gives doublet of doublets centered at 7.08 ppm ($J_{ab,bc}$ =6.8 Hz) and makes long range coupling with H_d (J_{bd} =1.2 Hz). H_c centered at 6.75 ppm which couples with H_b and H_d for triplet ($J_{cb,cd}$ =6.8 Hz) and makes long range coupling with H_a (J_{ca} =1.2 Hz). H_e protons give two singlets centered at 3.84 ppm for 3H and 3.82 ppm for 3H in the methylene groups bonded to oxygen atom and comes in low field compared to H_f because of the electron withdrawing substituents –OCOR. H_f protons give a singlet centered at 3.00 ppm which comes in high field compared to H_e protons because of bonded to nitrogen which is less electronegative atom than oxygen. (Figure 1.21)

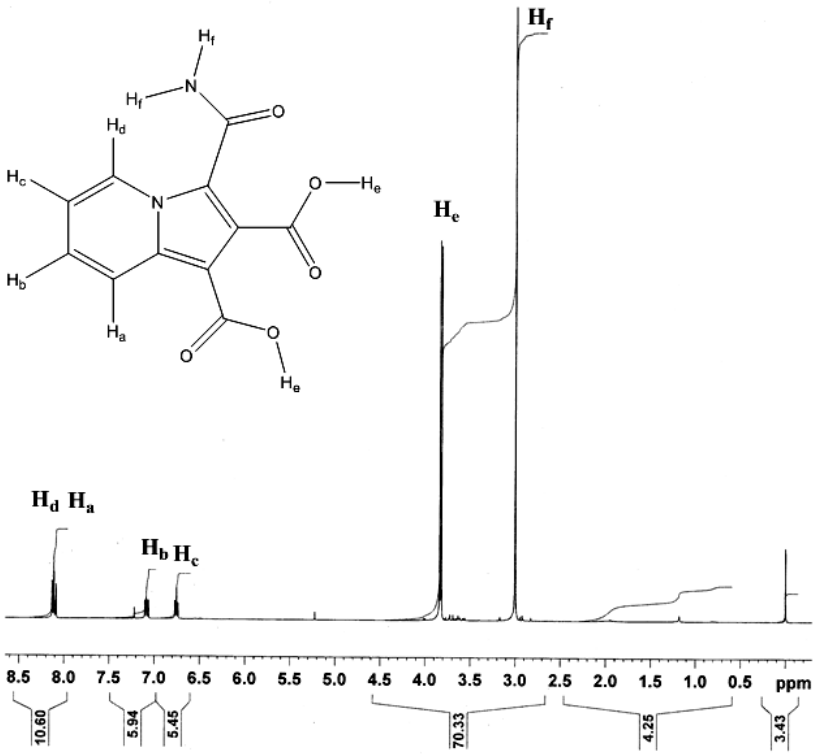


Figure 1. 21 The ^{1}H NMR Spectrum of 5a

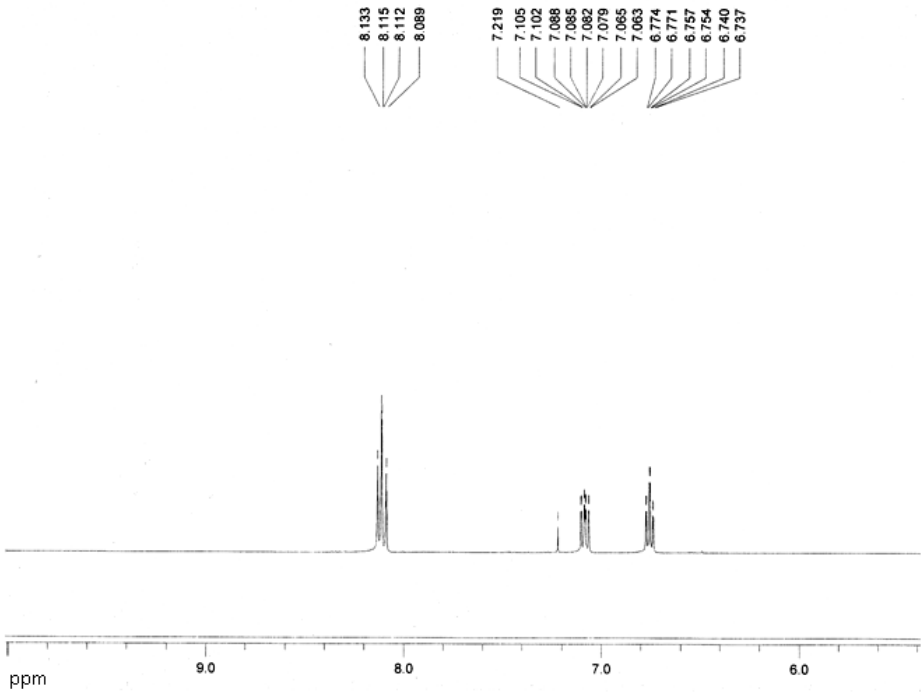


Figure 1. 22 Expanded (9.0-6.0 ppm) ^{1}H NMR Spectrum of 5a

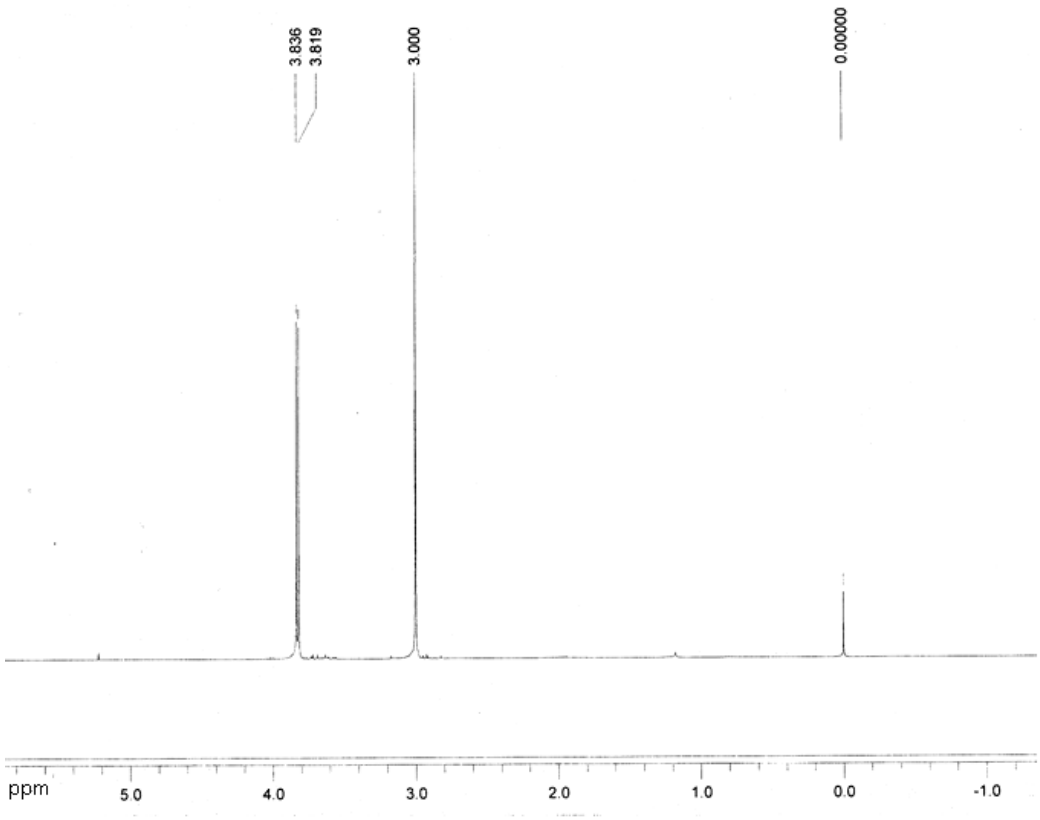


Figure 1. 23 Expanded (4.0-0.0 ppm) ^{1}H NMR Spectrum of 5a

According to the ^{13}C NMR spectrum of **5a**, there are fourteen carbon atoms related to the structure. The ^{13}C NMR spectrum shows signals for C_m carbon atom at 164.1 ppm, C_k carbon atom at 162.7 ppm, C_i carbon atom at 161.0 ppm. These three carbon atoms belong to the carbonyl carbon atom in the structure supporting the three carbonyl group in the structure. The C_e carbon atom show a signal at 135.0 ppm, C_g carbon atom at 124.6 ppm, C_d carbon atom at 123.2 ppm, C_h carbon atom at 120.9 ppm, C_a carbon atom at 119.2 ppm, C_b carbon atom at 113.1 ppm, C_c carbon atom at 101.3 ppm and C_f carbon atom at 95.1 ppm. These eight carbon atoms form the bridgehead aromatic structure of indolizine. The C_n carbon atom at 51.4 ppm and C_l carbon atom at 50.4 ppm.

These two carbons belong to the methylene group adjacent to the ester group. The C_j carbon atoms at 35.8 ppm which are the methyl groups bonded to nitrogen gives the same signal because of the environment.

Thanks to ^{13}C NMR spectrum of 5a, we can say clearly to be propped up the **5a** cycloadduct. (Figure 1.24)

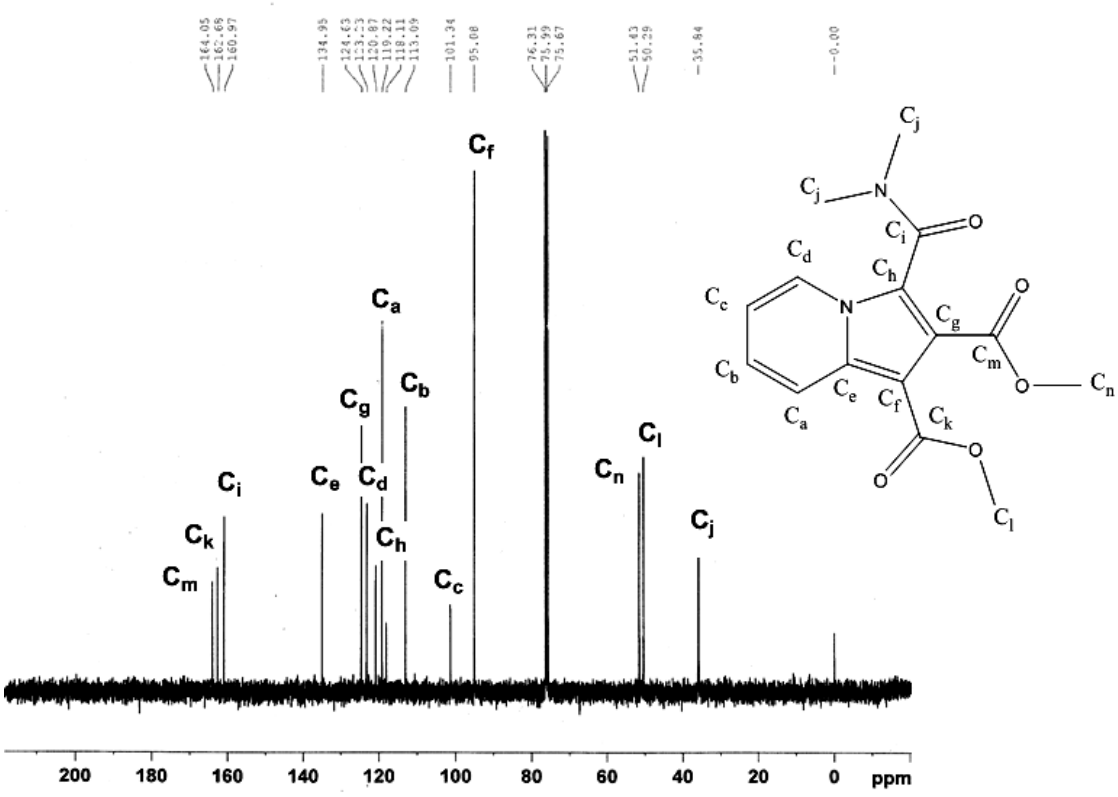


Figure 1. 24 The ^{13}C NMR Spectrum of 5a

3.1.2. Characterization of diethyl 7-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate (5f)

The cycloadduct **5f** is supported by the IR absorbtions for α,β-unsaturated ester groups [ν (neat) (C=O) 1728 and 1705 cm^{-1}], an amide group [ν (neat) (C=O) 1635 cm^{-1}] and a nitrile band [ν (neat) (C≡N) 2227 cm^{-1}]. (Figure 1.25)

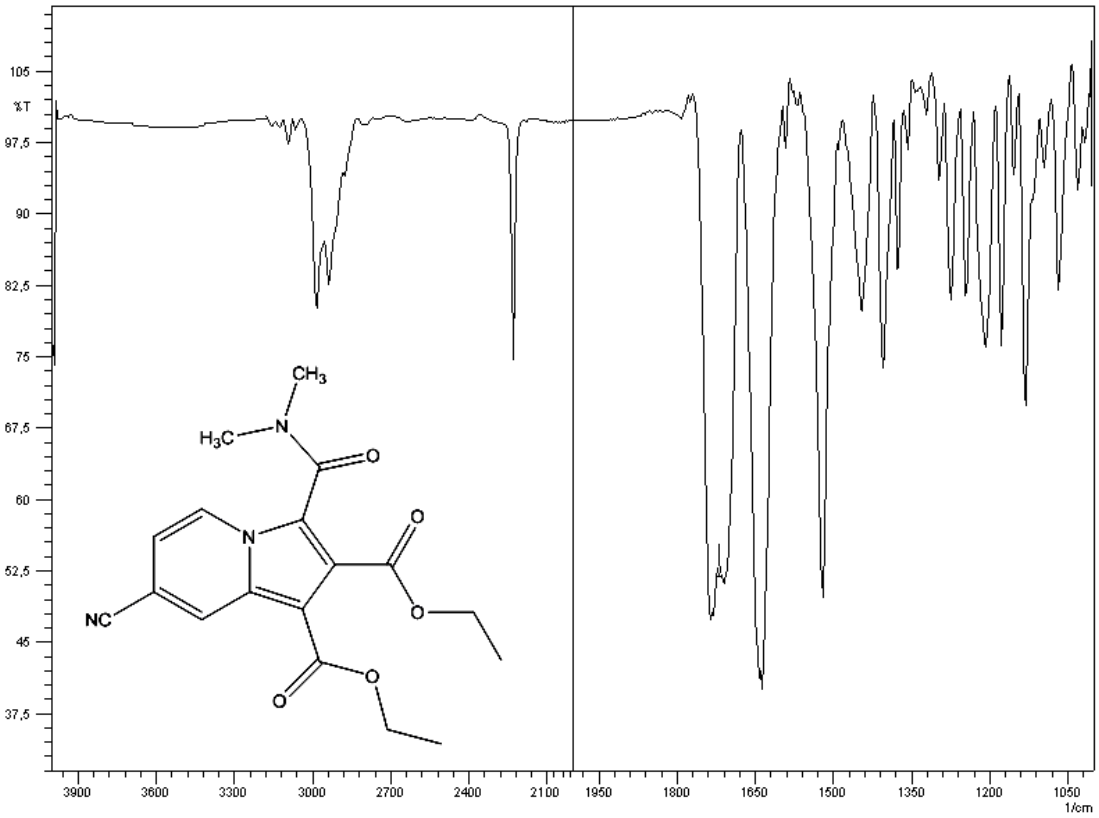


Figure 1. 25 The IR Spectrum of 5f

The ^{1}H NMR Spectrum of **5f** shows one singlet for H_a proton centered at 8.51 ppm. The H_c proton gives doublet of doublet making vicinal coupling with H_b (J_{cb}= 7.2 Hz) which is centered at 8.17 ppm and long range coupling with H_a (J_{ca}= 1.2 Hz) which are para position to each other. The H_b proton centered at 6.84 ppm gives a doublet of doublet coupling with H_c (J_{bc}=7.6 Hz) and also makes long range coupling with H_a (J_{ba}= 1.8 Hz) which are meta position in the indolizine ring. The positions of the protons in the heterocyclic aromatic compound indicates why coupling constant of J_{ba} is higher than J_{ca}. Using the coupling constants values and chemical shifts originated from substituents effects in the indolizine ring, these three protons are placed correctly. The H_d protons centered at 4.32 ppm give multiplet coupling with H_e on the other hand H_f protons give a singlet centered at 3.00 ppm. H_e couples with H_d giving multiplet in ^{1}H NMR spectrum centered at 1.31 ppm. Thanks to ^{1}H NMR spectrum, the protons are characterized supporting the structure **5f** is true for the cycloadduct. (Figure 1.26)

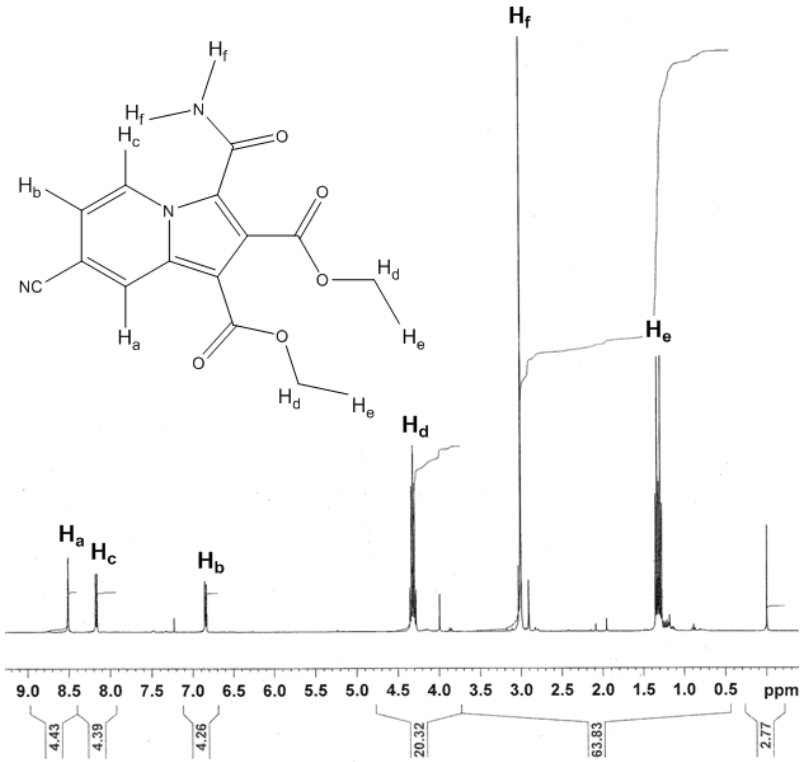


Figure 1. 26 The [1]H NMR Spectrum of 5f

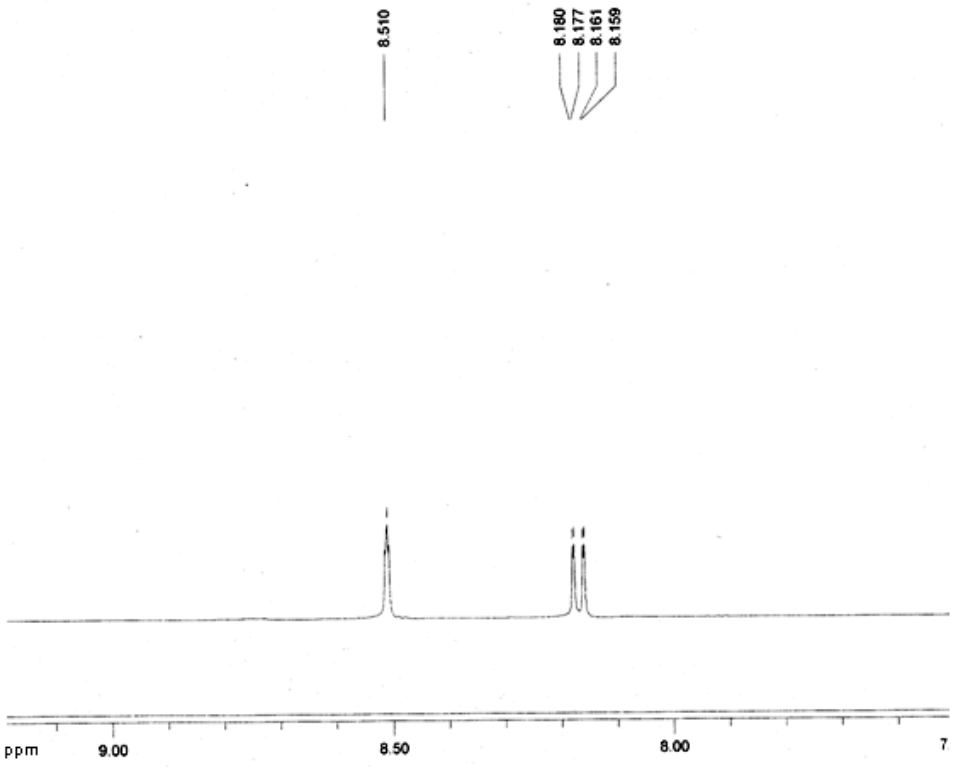


Figure 1. 27 Expanded (9.0 -8.0 ppm) [1]H NMR Spectrum of 5f

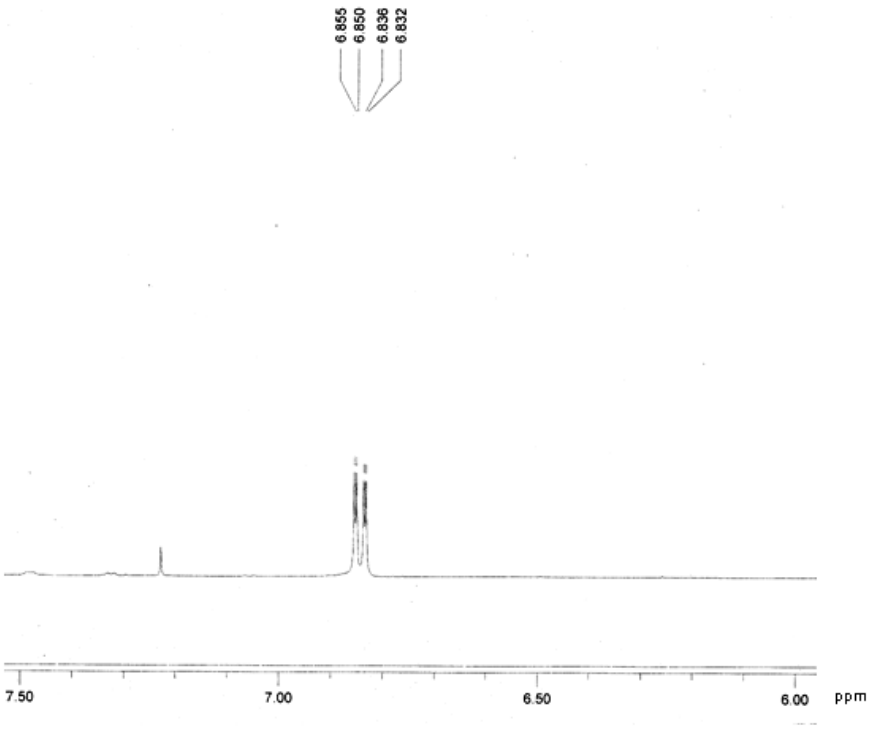


Figure 1. 28 Expanded (7.5-6.0 ppm) ^{1}H NMR Spectrum of 5f

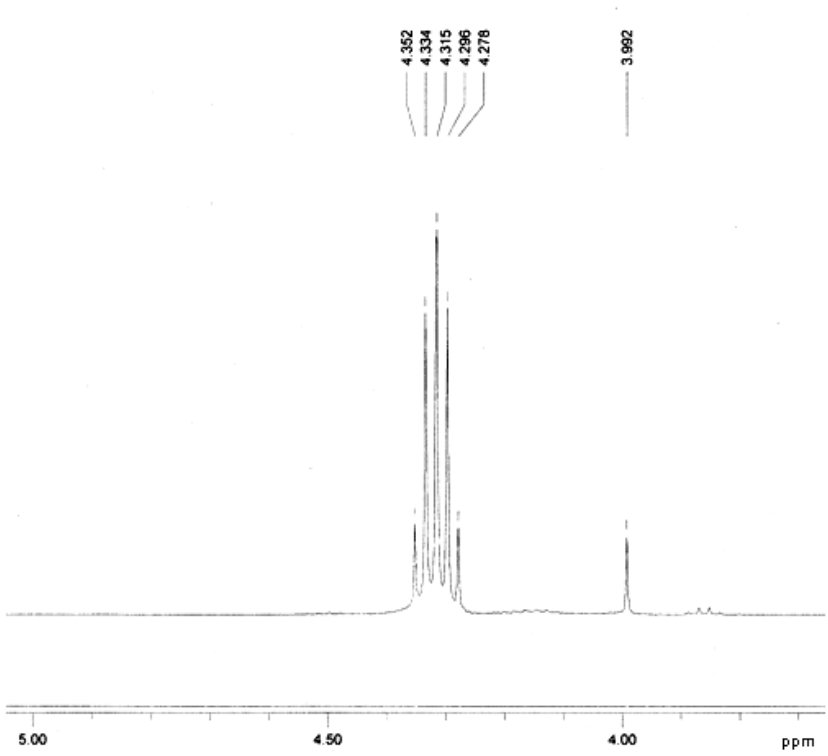


Figure 1. 29 Expanded (5.0-4.0 ppm) ^{1}H NMR Spectrum of 5f

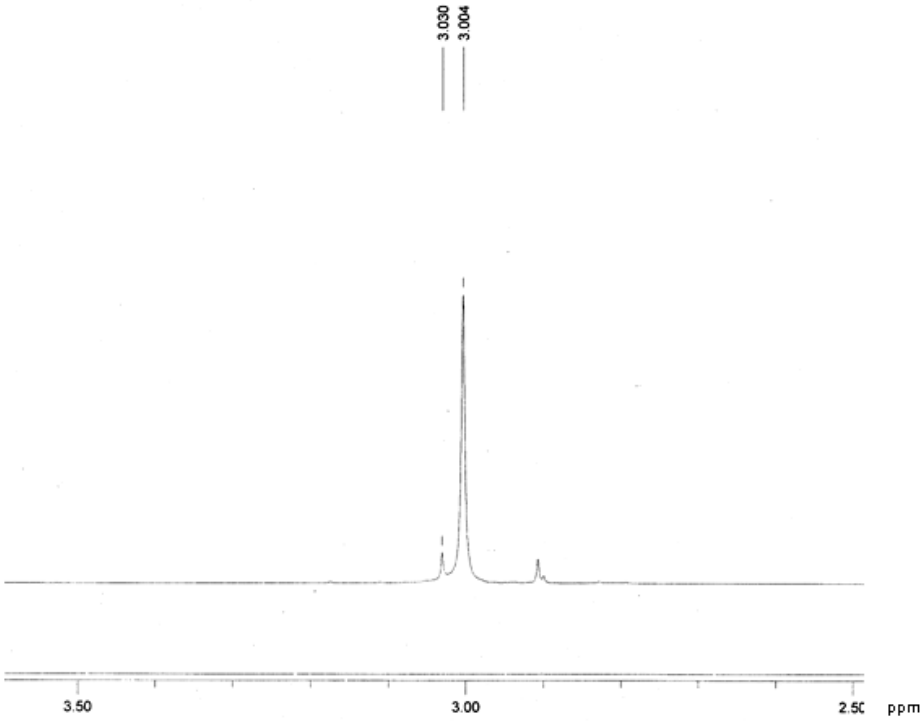


Figure 1. 30 Expanded (3.5-2.5 ppm) ^{1}H NMR Spectrum of 5f

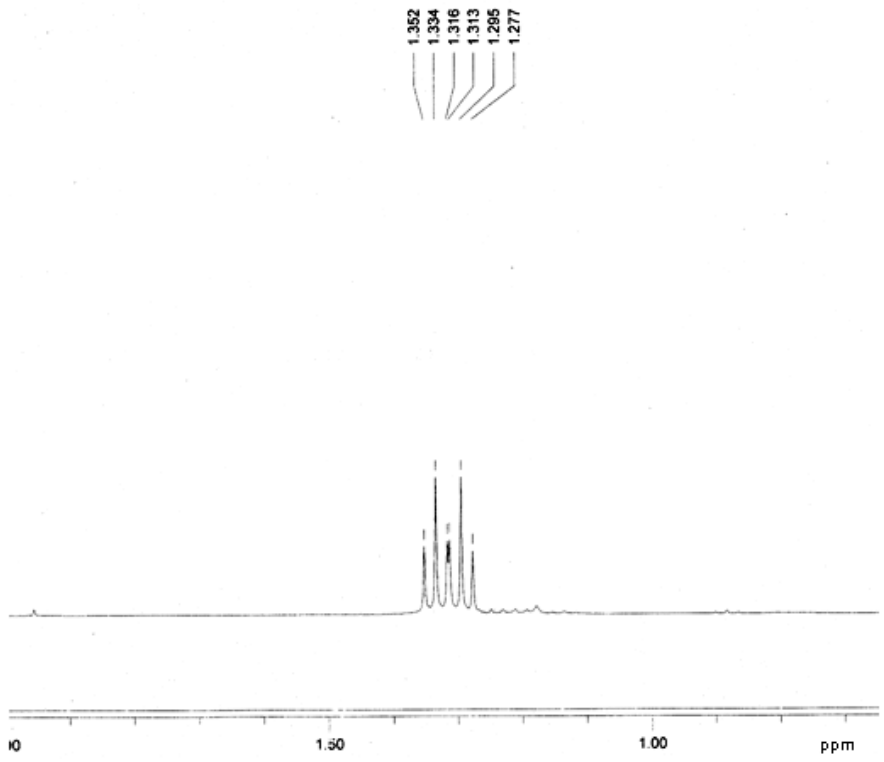


Figure 1. 31 Expanded (1.5-1.0 ppm) ^{1}H NMR Spectrum of 5f

The ^{1}H NMR spectroscopy is a quantitative method for estimating certain nuclei while ^{13}C NMR spectroscopy gives information about the carbon skeleton. The most important difference between the proton and carbon spectra of the magnetic susceptibility of carbon and chemical setting of the scarcity value. When looking at ^{13}C NMR spectrum, eighteen carbon atoms are clearly seen both the 5f cycloadduct and the spectrum. This spectrum shows signals for C_p carbon atom at 162.7 ppm, C_m carbon atom at 161.6 ppm, C_j carbon atom at 160.2 ppm, C_f carbon atom at 132.2 ppm, C_h carbon atom at 126.2 ppm, C_c carbon atom at 125.5 ppm, C_d carbon atom at 122.6 ppm, C_i carbon atom at 120.8 ppm, C_a carbon atom at 116.5 ppm, C_e carbon atom at 112.8 ppm, C_g carbon atom at 106.1 ppm, C_b carbon atom at 95.4 ppm, C_r carbon atom at 61.0 ppm, C_n carbon atom at 60.0 ppm, C_k carbon atom at 40.3 ppm, C_l carbon atom at 36.1 ppm, C_s carbon atom at 13.5 ppm and C_o carbon atom at 13.3 ppm. Accordingly, we can propose that the **5f** cycloadduct is supported by spectroscopic method of ^{13}C NMR spectrum in addition to IR and ^{1}H NMR Spectrum. (Figure 1.32)

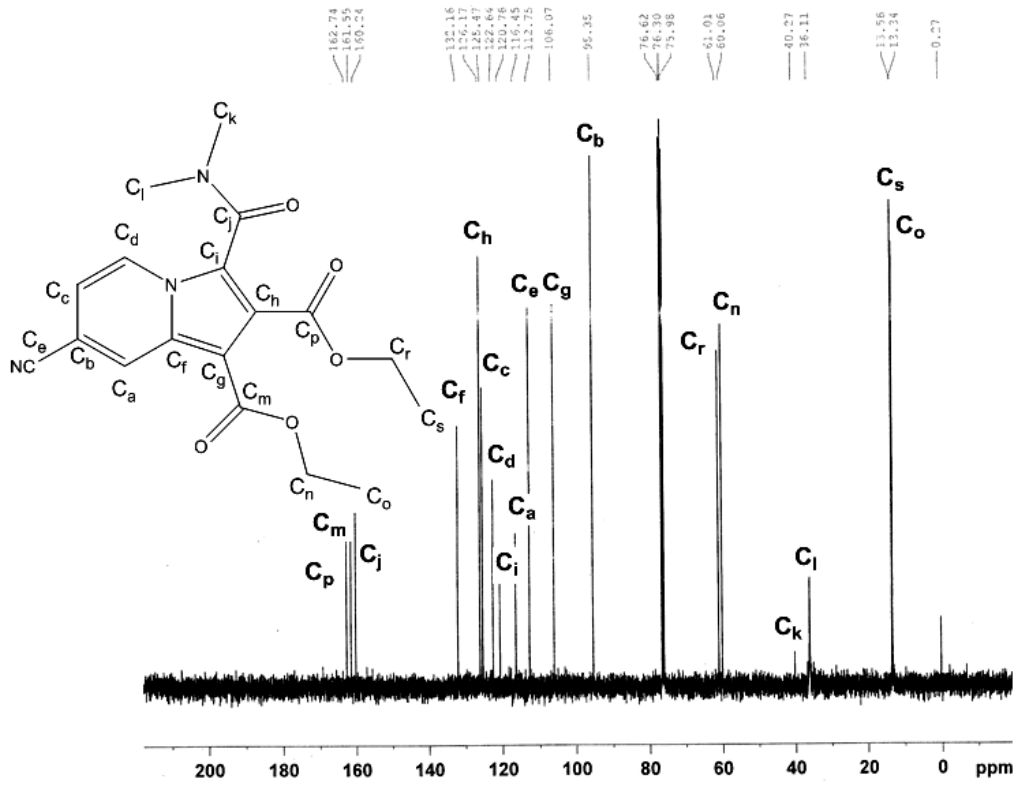


Figure 1. 32 The ^{13}C NMR Spectrum of 5f

^{13}C atoms chemical shifts are more sensitive than ^{1}H atoms to substituents which are place of β- and γ-positions. Therefore, various formulas have been developed based on the principle of substituent effects to gather more participants in order to calculate ^{13}C chemical shifts [129-131].

$\delta_C = -2.3 + \sum z_i$ for sp^3 carbons

$\delta_C = 123.3 + \sum z_i^{\alpha} + \sum z_i^{\alpha'} + \sum S$ for sp^2 carbons

$\delta_C = 128.5 + \sum z_i$ for benzene

$\delta_C = 166 + \sum z_i + E$ for ester carbonyl carbons

$\delta_C = 165 + \sum z_i + N$ for carboxylic amides

According to the above equation some calculations have been made and the approximate δ values have been found in ppm

S = Steric correction

E = Substituents effects for esters

N = Substituents effect for amides

$\delta_{Cs\ ,\ Co}$ = -2.3 + $\sum z_i$

= -2.3 + Z $_{\alpha\text{-}CH_3}$ + Z $_{\beta - O}$ + Z $_{\gamma\text{-}COR}$

= -2.3 + 9.1 + 10.1 -3.0

= 13.9 ppm (observed 13.5 ppm)

$\delta_{Cr\ ,\ Cn}$ = -2.3 + $\sum z_i$

= -2.3 + Z $_{\alpha\text{-}CH_3}$ + Z $_{\beta - O}$ + Z $_{\gamma\text{-}COR}$

= -2.3 + 9.1 + 49 + 3

= 58.8 ppm (observed 60.0 ppm)

δ_{Ce} = 128.5 + $\sum z_i$

= 128.5 + Z $_{i\text{-}CN}$ + Z $_{o - H}$

= 128.5 – 16.0

= 112.5 ppm (observed 112.8 ppm)

$\delta_{Cm\ ,\ Cp}$ = 166 + $\sum z_i$ + E

= 166 + $Z_{i\ -\ CH_3}$ + E

= 166 + 11 – 14

= 163 ppm (observed 162.1 ppm)

$\delta_{Ck\ ,\ Cl}$ = -2.3 + $\sum z_i$

= -2.3 + $Z_{\alpha\ –\ NCO}$ + $Z_{\beta\ -\ N\ –}$

= -2.3 + 22.0 + 18.0

= 37.7 ppm (observed 38.2 ppm)

δ_{Ca} = 128.5 + $\sum z_i$

= 128.5 + $Z_{i\ –\ H}$ + $Z_{o\ –\ C\ –\ N\ -}$ + $Z_{o\ –\ N}$ + $Z_{m\ –\ H}$ +

= $Z_{m\ –\ N\ -}$ + $Z_{p\ –\ H}$

= 128.5 + 3.5 – 15.7 + 0.8

= 117.1 ppm (observed 116.5 ppm)

δ_{Cb} = 128.5 + $\sum z_i$

= 128.5 + $Z_{i-N-C} + Z_{o-H} + Z_{m-H} + Z_{m-CH_3} + Z_{p-N-}$

= 128.5 - 16.0 – 11.8

= 98.9 ppm (observed 95.3 ppm)

δ_{Cc} = 128.5 + $\sum z_i$

= 128.5 + $Z_{i-H} + Z_{o-C-N-} + Z_{o-H} + Z_{m-H} + Z_{m-N-} +$

= Z_{p-CH_3}

= 128.5 + 3.5 + 0.8 + 7.0

= 125.8 ppm (observed 125.5 ppm)

δ_{Cd} = 128.5 + $\sum z_i$

= 128.5 + $Z_{i-H} + Z_{o-H} + Z_{o-N-} + Z_{m-C-N} + Z_{m-CH_3} +$

= Z_{p-COOR}

= 128.5 + 0.7 – 16.5 + 10.2

= 122.5 ppm (observed 122.6 ppm)

δ_{Cf} $= 123.3 + \sum z_i^{\alpha} + \sum z_i^{\alpha'} + \sum S$

$= 123.3 + Z_{\alpha - CH_3} + Z_{\alpha - N^-} + Z_{\alpha' - COOR}$

$= 123.3 + 10.6 - 15.4 + 14.0$

$= 132.8$ ppm (observed 132.2 ppm)

δ_{Cg} $= 123.3 + \sum z_i^{\alpha} + \sum z_i^{\alpha'} + \sum S$

$= 123.3 + Z_{\alpha - COOR} + Z_{\alpha' - N^-} + Z_{\alpha - COOR}$

$= 123.3 + 6.3 - 29.2 + 6.3$

$= 106.7$ ppm (observed 106.1 ppm)

δ_{Ch} $= 123.3 + \sum z_i^{\alpha} + \sum z_i^{\alpha'} + \sum S$

$= 123.3 + Z_{\alpha - COOR} + Z_{\alpha' - RCON^-} + Z_{\alpha' - C - N^-} + Z_{\alpha - CH_3}$

$= 123.3 + 6.3 - 29.2 + 14.2 + 10.6$

$= 125.2$ ppm (observed 126.2 ppm)

δ_{Cj} $= 165 + \sum z_i + N$

$= 165 + Z_{i - CH_3} + N$

$= 165 - 1.5 - 1.5$

$= 162$ ppm (observed 160.2 ppm)

3.1.3. Characterization of diethyl 6-cyano-3-(dimethylcarbamoyl)indolizine-1,2-dicarboxylate (5d)

The cycloadduct **5d** is supported by the IR absorbtions for α,β-unsaturated ester groups [ν (neat) (C=O) 1735 and 1701 cm^{-1}], an amide group [ν (neat) (C=O) 1639 cm^{-1}] and a nitrile band [ν (neat) (C≡N) 2233 cm^{-1}]. (Figure 1.33)

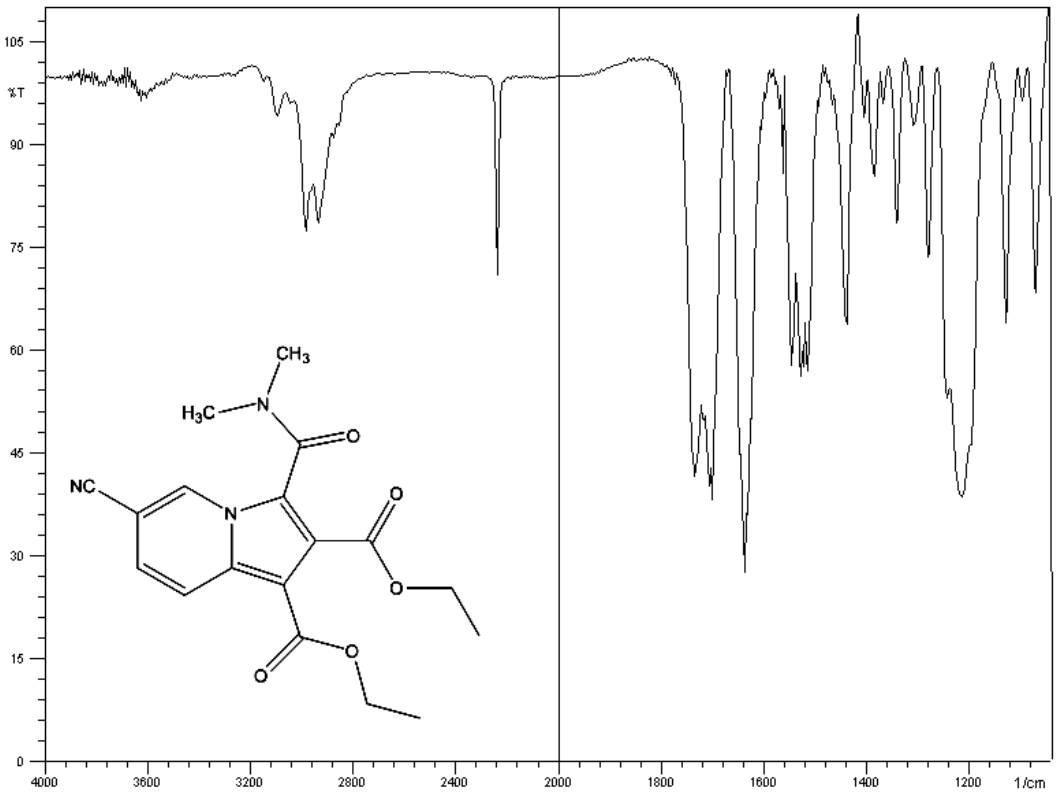


Figure 1. 33 The IR Spectrum of 5d

The ^{1}H NMR spectrum of **5d** shows us the structure 5d includes six types of protons which are H_a, H_b, H_c, H_d, H_e and H_f. The ^{1}H NMR spectrum of cycloadduct 5d shows one singlet which indicates H_c centered at 8.65. H_a and H_b protons show doublet of doublets centered at 8.20 ppm and 7.13 ppm. H_a proton only make vicinal coupling with H_b (J_{ab}= 10.4 Hz). The vicinal coupling can have values 0-16 Hz depending mainly on the dihedral angle which is known as Karplus relationship. When the dihedral angle between two vicinal protons is near 0^o or 180^o, the coupling constant will be relatively large. It is based on the this relationship, we can say clearly that the dihedral angle between the protons are near to 0^o. H_a proton and H_b proton are ortho position in the aromatic ring and therefore we expect the coupling constant values between the 6-10 Hz. H_a proton also makes long range coupling with H_c (J_{ac}= 1.2 Hz) which are para position in the indolizine ring. H_b proton shows doublet of doublets coupling with H_a (J_{ba}= 10.8 Hz) and long range coupling with H_c (J_{bc}= 1.4 Hz) which are ortho position in the indolizine ring. Therefore J_{bc} is higher than J_{ac} because of the position of the protons in the aromatic ring. Similarly, in condensed polynuclear aromatic compounds and heterocyclic compounds the magnitude of the coupling constants between protons in the aromatic ring reflects the relative position of the coupled protons. H_d protons show multiplet that centered at 4.31 ppm. H_f protons bonded to nitrogen atom give a singlet centered at 3.03 ppm due to the same environment. H_e protons give multiplet centered at 1.31 coupling with H_d. Accordingly, we can say that ^{1}H NMR supports the **5d** cycloadduct.(Figure 1.34)

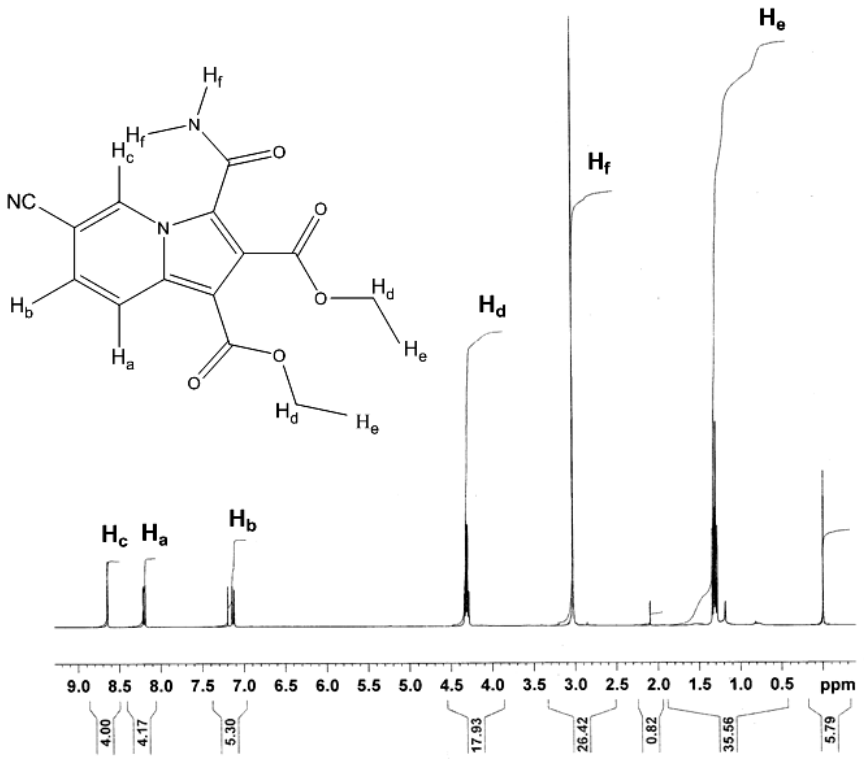


Figure 1. 34 The ^{1}H NMR Spectrum of 5d

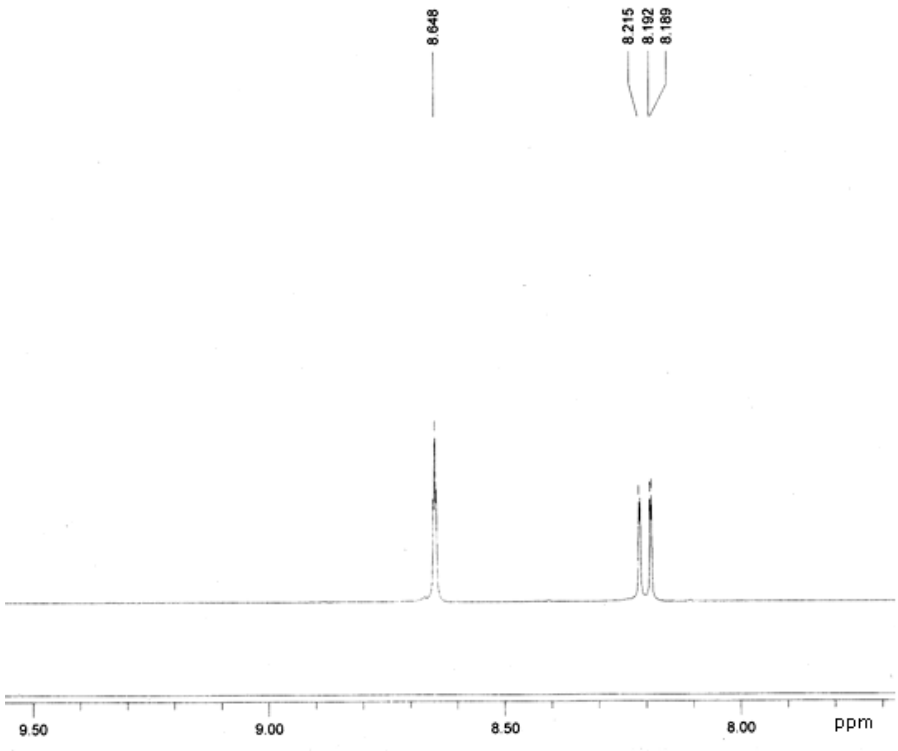


Figure 1. 35 Expanded (9.5-8.0 ppm) ^{1}H NMR Spectrum of 5d

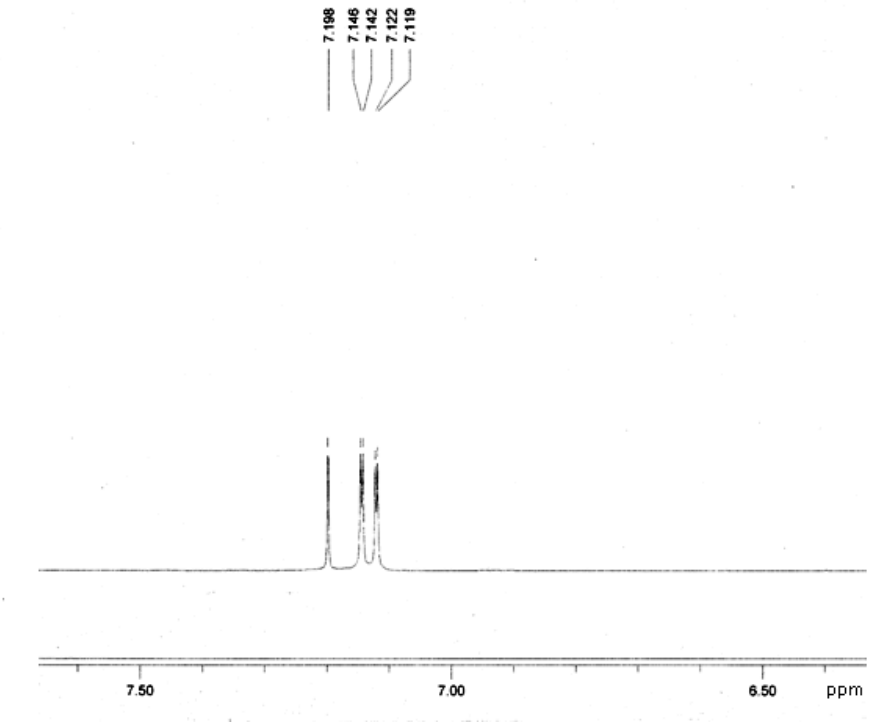


Figure 1. 36 Expanded (7.5-6.5 ppm) ^{1}H NMR Spectrum of 5d

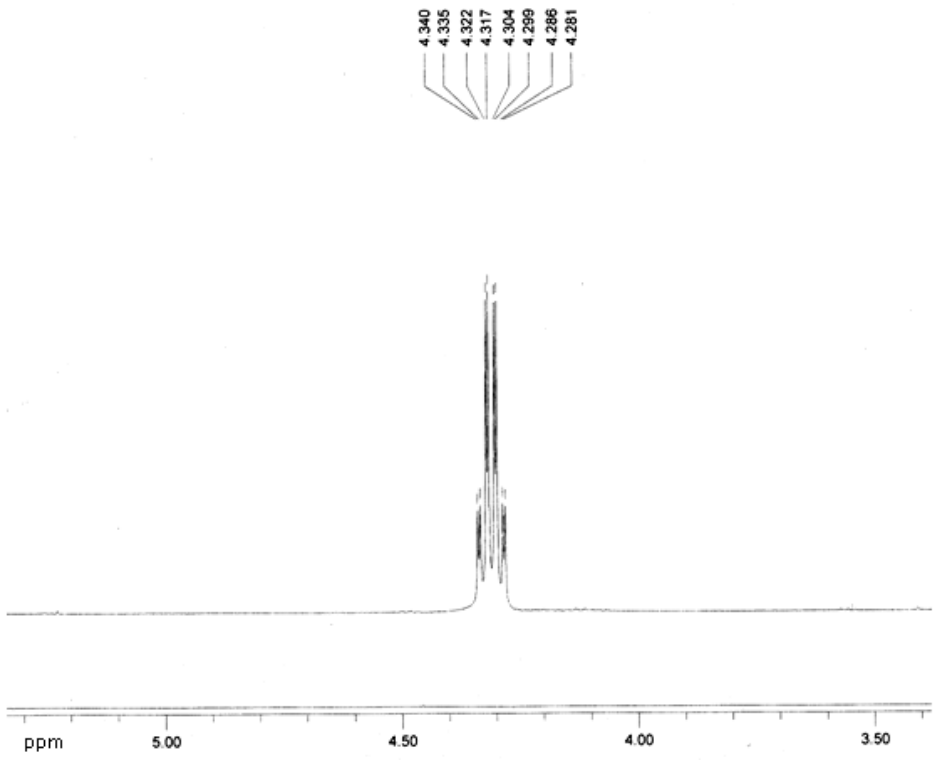


Figure 1. 37 Expanded (5.0-3.5 ppm) ^{1}H NMR Spectrum of 5d

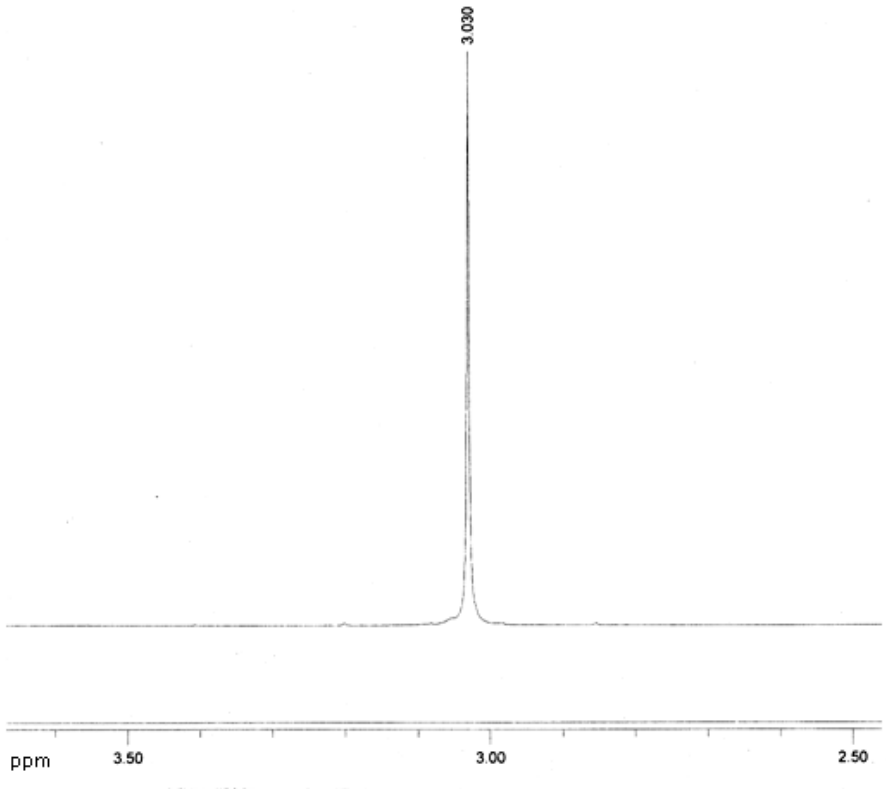


Figure 1. 38 Expanded (3.5-2.5 ppm) ^{1}H NMR Spectrum of 5d

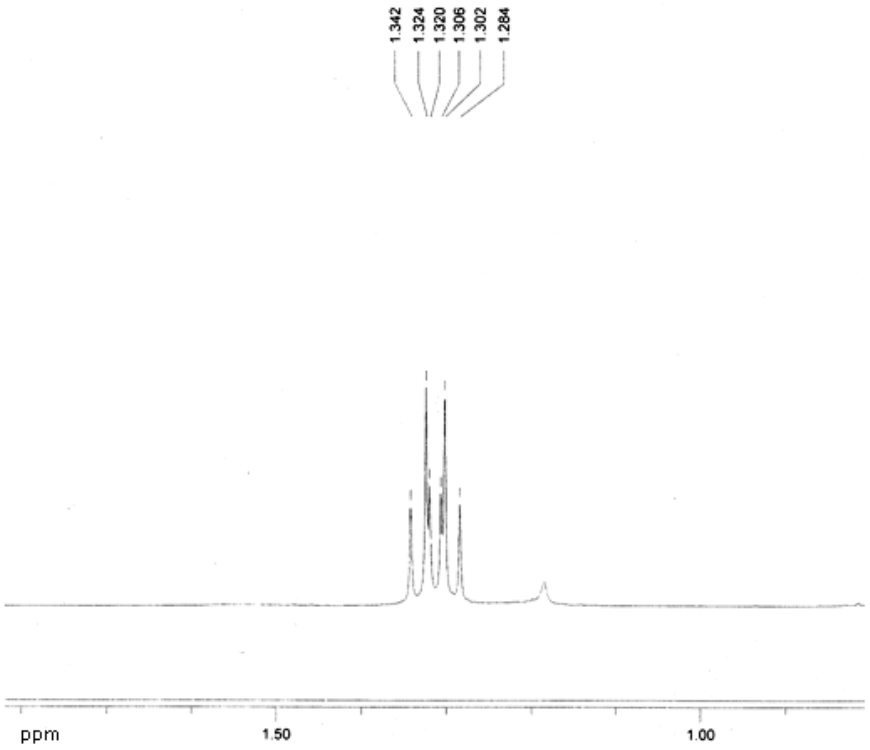


Figure 1. 39 Expanded (1.5-1.0 ppm) ^{1}H NMR Spectrum of 5d

According to the ^{13}C NMR spectrum of **5d**, there are seventeen carbon atoms related to the structure. The ^{13}C NMR spectrums shows signals for C_o cabon atom at 162.4 ppm, C_l carbon atom at 161.2 ppm, C_j carbon atom at 159.7 ppm. These three carbon atoms indicate that the structure includes three carbonyl groups. The C_f carbon atom shows a signal at 133.6 ppm, C_h carbon atom at 130.9 ppm, C_d carbon atom at 123.7 ppm, C_i carbon atom at 121.7 ppm, C_b carbon atom at 119.9 ppm, C_a carbon atom at 118.5 ppm, C_e carbon atom at 114.6 ppm, C_g carbon atom at 103.9 ppm and C_c carbon atom at 94.8 ppm. These nine carbon atoms indicates the structure of inolizine ring. The ^{13}C NMR spectrums continues to give signals for C_p carbon atom at 60.5 ppm, C_m carbon atom at 59.3 ppm, C_k carbon atom at 35.8 ppm, C_r carbon atom at 12.9 ppm and C_n carbon atom at 12.78 ppm. These five carbon atoms complete the number of carbon atoms to give the structure 5d. Thereby, we can propose that the **5d** cycloadduct is supported by spectroscopic method of ^{13}C NMR spectrum in addition to IR and ^{1}H NMR Spectrum. (Figure 1.40)

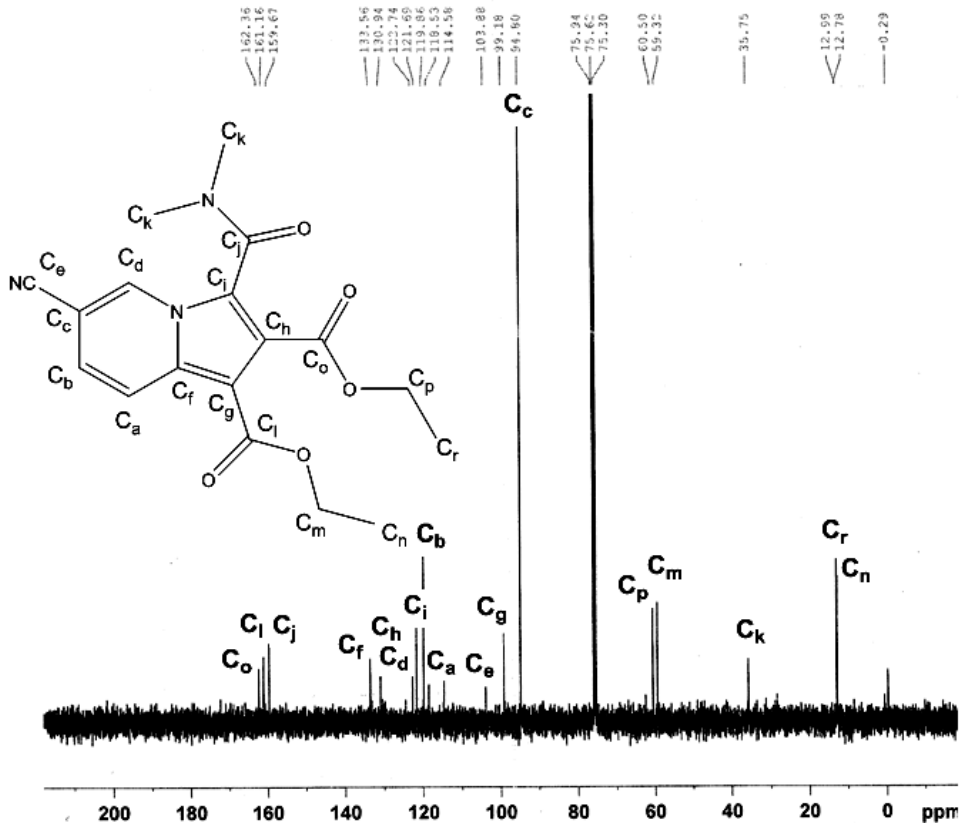


Figure 1. 40 The ^{13}C NMR Spectrum of 5d

3.2. Molecular Orbital Considerations

The computational methods, both AM1 and PM3, were used to get the related data on the frontier molecular orbital energies and their coefficients of substituted an unsubstituted ylides and dipolarophiles. These calculations were carried out using HyperChem 7.0 program package.

Table 1 shows the HOMO and LUMO energies of the ylides and dipolarophiles. The additional data were also given on the coefficients of the atoms on the reactive sites for them. Table 2 show the relative energy differences of the frontier molecular orbitals.

Both methods, AM1 and PM3, reveal that according to the unsubstituted ylide p-dimethylamino pyridine ylide denoted as having the electron donating group, was found to have higher HOMO and LUMO energies. On the other hand, the ylides having electron withdrawing groups such as 3-CN and 4-CN substituted ones, had lower HOMO and LUMO energies with respect to unsubstituted pyridine ylide. Of course, that is a general tendency of both electron donating and electron withdrawing groups raising and decreasing the HOMO and LUMO energies. But the lowering effect of the electron withdrawing groups on the LUMO seems to be somewhat more than that on the HOMO(see table 2). Another evidence seen by means of these calculations was that the PM3 calculations gave much lowering effect on the LUMO and HOMO energies of the pDMA pyridine ylide, that is the electron donating substituted one.

The situation was somewhat complex for dipolarophiles when PM3 calculations were considered. There were an increasing effect of AM1 and PM3 on the HOMO and LUMO energies of DMAD, DEAD, and VA. But there can be seen a decreasing effect on the LUMO and HOMO of PA and DPA.

Table 1 The FMO data of the ylides and dipolarophiles

AM1	**HOMO**	**LUMO**	**PM3**	**HOMO**	**LUMO**
Py. ylide			**Py. ylide**		
Eigenvalue	-7.64844	-0.43669	Eigenvalue	-8.01551	-0.46955
Pz C 6	-0.70272	-0.36378	Pz C 6	-0.67653	-0.31574
Pz C 8	0.36818	-0.19451	Pz C 8	0.35879	-0.05602
3CN Py. ylide			**3CN Py. ylide**		
Eigenvalue	-7.98000	-1.02031	Eigenvalue	-8.35773	-1.14332
Pz C 6	0.69527	0.28743	Pz C 6	-0.66418	-0.20185
Pz C 8	**-0.37840**	**-0.13373**	**Pz C 8**	**0.36590**	**0.26681**
Pz C 12	-0.36480	0.48151	Pz C 12	0.36657	-0.47771
4CN Py. ylide			**4CN Py. ylide**		
Eigenvalue	-8.05176	-1.10656	Eigenvalue	-8.40787	-1.13985
Pz C 6	-0.66653	0.40408	Pz C 6	0.64239	-0.36575
Pz C 8	0.37852	0.18505	Pz C 8	-0.36316	-0.15156
4DMA Py.ylide			**4DMA Py.ylide**		
Eigenvalue	-7.05672	-0.19726	Eigenvalue	-7.69965	-0.49415
Pz C 6	-0.68783	-0.29750	Pz C 6	-0.63363	0.27956
Pz C 8	0.29547	-0.09772	Pz C 8	0.30824	0.03928
DEAD			**DEAD**		
Eigenvalue	-11.61997	-0.78318	Eigenvalue	-11.58975	-0.63158
Pz C 1	-0.04460	0.47303	Pz C 1	0.00579	0.46065
Pz C 2	-0.05255	-0.48084	Pz C 2	0.00786	-0.46983
DMAD			**DMAD**		
Eigenvalue	-11.96085	-0.92905	Eigenvalue	-11.82864	-0.77047
Pz C 1	0.00058	-0.47941	Pz C 1	0.00000	-0.47075
Pz C 2	-0.00035	0.47942	Pz C 2	0.00000	0.47067
	(**NHOMO**)			(**NHOMO**)	
Eigenvalue	-11.96340		Eigenvalue	-11.85073	
Pz C 1	0.00411		Pz C 1	0.11624	
Pz C 2	0.00413		Pz C 2	0.11577	
PA			**PA**		
Eigenvalue	-9.28994	0.00092	Eigenvalue	-9.39638	-0.080092
Pz C 1	0.40602	0.35932	Pz C 1	-0.38847	0.35362
Pz C 2	0.24803	-0.20857	Pz C 2	-0.23501	-0.20511
DPA			**DPA**		
Eigenvalue	-8.75060	-0.44438	Eigenvalue	-8.89559	-0.51165
Pz C 1	-0.35288	0.32292	Pz C 1	-0.34224	0.31919
Pz C 2	-0.35288	-0.32292	Pz C 2	-0.34224	-0.31919
VA			**VA**		
Eigenvalue	-10.03781	0.56444	Eigenvalue	-10.03643	0.52026
Pz C 1	-0.66989	-0.50969	Pz C 1	-0.66881	0.51439
Pz C 2	-0.54080	0.46734	Pz C 2	-0.53519	-0.47997

The unit of HOMO and LUMO is eV.

Table 2 The relative energies of the HOMO and LUMO orbitals calculated by AM1 and PM3(*PM3 calculations)

0.56444**(0.52026)***
VA
0.00092**(-0.080092)***
PA
-0.19726**(-0.47978)***
pDMA Py.ylide
-0.43699**(-0.46955)***
Py.ylide
-0.44438**(-0.51165)***
DPA

-0.78318**(-0.63152)***
DEAD
-0.92905**(-0.77047)***
DMAD
-1.01955**(-1.14332)***
3CN Py.ylide
-1.10659**(-1.13985)***
4CN Py.ylide

LUMO

HOMO

-7.05672**(-7.69438)***
pDMA Py.ylide
-7.64826**(-8.01551)***
Py.ylide
-7.98000**(-8.35773)***
3CN Py.ylide
-8.05176**(-8.40787)***
4CN Py.ylide
-8.75060**(-8.89559)***
DPA
-9.28994**(-9.39638)***
PA
-10.03781**(-10.0643)***
VA

-11.61997**(-11.58975)***
DEAD
-11.96340**(-11.85073)***
DMAD

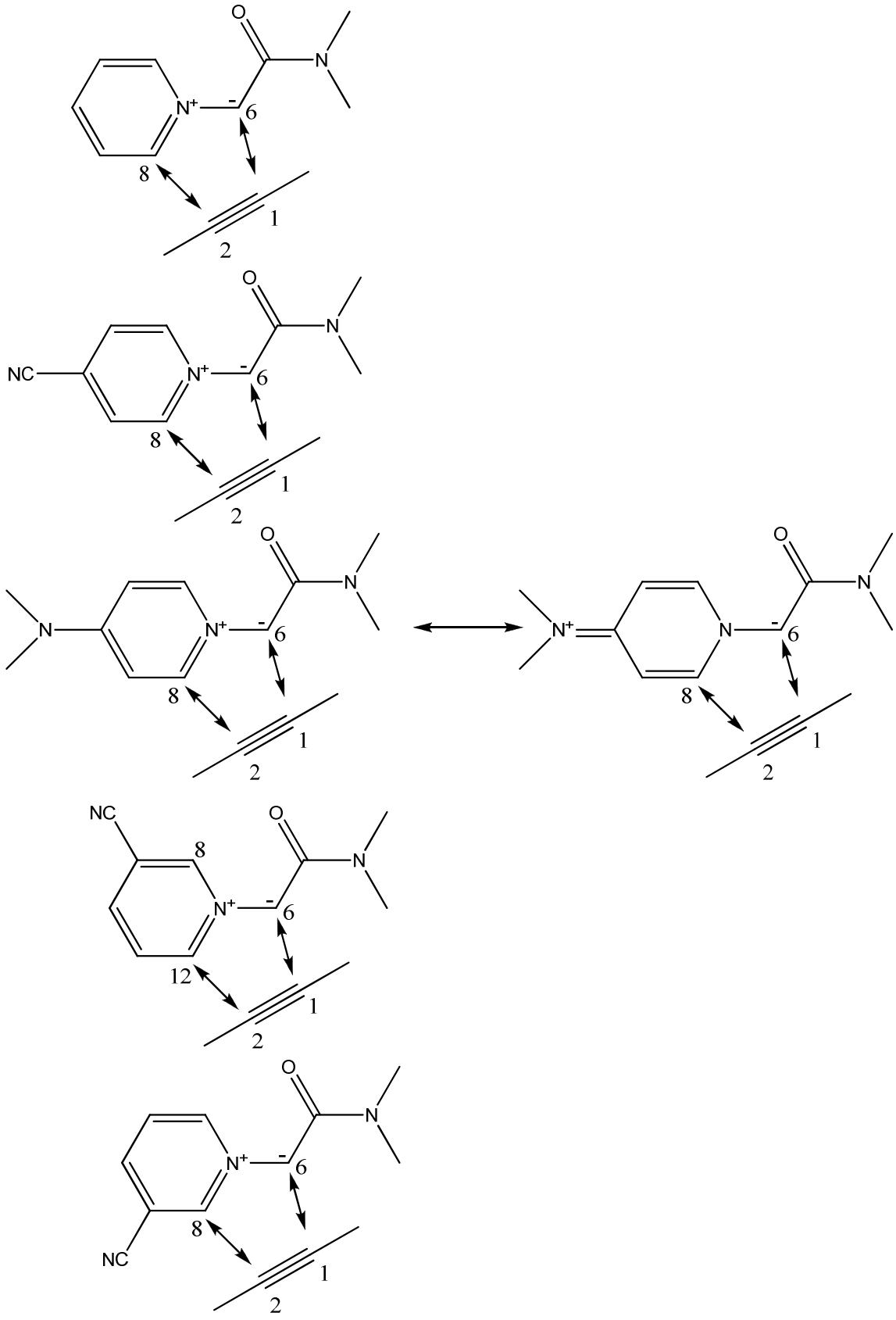
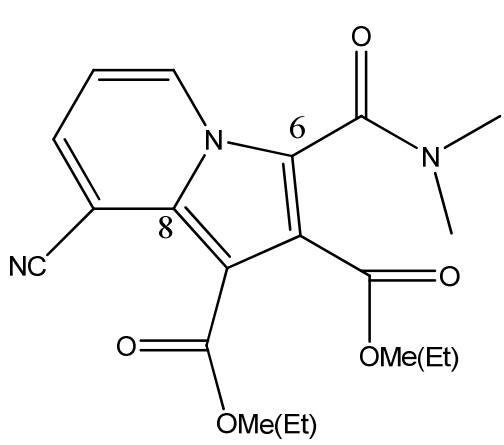
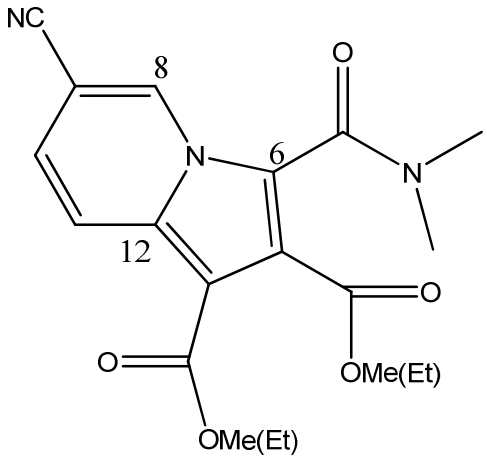


Figure 1. 41 The reactive sides of the ylides

There are two regioisomeric cases for 3CN substituted pyridine ylide as being unsymmetrical dipole (see figure 1.41). As figure 1.42 indicates two regioisomers there can be obtained for symmetrical dipolarophiles. Among them the experimental findings favored the regioisomers II





regioisomer I regioisomer II

Figure 1. 42 Possible regioisomers

According to Sustmann's equation [132] below the prediction of which regioisomer would predominantly form from the interaction between the HOMO of one reactant and theLUMO of the other would be possible.

$$\Delta E = \frac{2(C_r^{HOMO}C_s^{LUMO} + C_t^{HOMO}C_u^{LUMO})^2\gamma^2}{E_{ylide}^{HOMO} - E_{dipolarophile}^{LUMO}} + \frac{2(C_r^{LUMO}C_s^{HOMO} + C_t^{LUMO}C_u^{HOMO})^2\gamma^2}{E_{dipolarophile}^{HOMO} - E_{ylide}^{LUMO}}$$

In this equation, C_r and C_t are the MO coeficients of the interaction sites of one and C_s and C_u are the MO coefficients of the interaction sites of the second at the level of the frontier MO's.

The other feature of the these reactions is that they can be either $HOMO_{dipole}$-$LUMO_{dipolarophile}$ or $LUMO_{dipole}$-$HOMO_{dipolarophile}$ controlled. If the data of table 1 is carefully analyzed the reactions are easily seen to be $HOMO_{dipole}$-$LUMO_{dipolarophile}$ controlled. The first part of the equation gives $HOMO_{dipole}$-$LUMO_{dipolarophile}$ contribution and the second part is due to the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ contribution.

AM1 type calculations indicate that there is nearly zero contribution of the second part. At the PM3 type calculations the second part make relatively less contribution to the total energy measuring the transition state stabilization during the bond formation process. The larger value of ΔE means that the reaction is more ready.

Using the values of AM1 method, as the prediction of the regioisomers of 3CN substituted pyridine ylide we calculated $\Delta E/\gamma^2$ values for only DMAD. The $\Delta E/\gamma^2$ value for regioisomer I, formed from C6-C8 interaction sites, is 0.07515 and for regioisomer II, formed from C6-C12 interaction sites(see figure 1.42), the $\Delta E/\gamma^2$ value is 0.07317. That means AM1 method favors the formation of the regioisomer I. But the same equation using PM3 method led to larger $\Delta E/\gamma^2$ value for the regioisomer II having 0.063717 over that of the regioisomer I that is 0.062605. We concluded that PM3 method would be a better one over AM1 on the basis of experimental findings.

We obtained cycloadducts only from dipolarophiles DMAD and DEAD with unsubstituted and 3CN and 4CN substituted pyridine ylides due to lower energy diffferences between their LUMO and HOMO's respectively that is the usual case if their energies are compared Among them the unsubstituted pyridine ylide was found to be more reactive due to lower HOMO ylide-LUMO dipolarophile energy gap. But overall energy gap analysis pDMA pyridine ylide seems to be somewhat more reactive because its HOMO level in energy is closer to the LUMO levels of the dipolarophiles than over the others. But it is found experimentally to be less reactive than that of the other ylides. The reason can be given to the second resonance structure of it(see figure 1.41) in which the dipole appearance of the desired positions C6 and C8 would be lost.

However we can conclude that FMO approach appears to be a relatively powerful tool to predict the course of the cycloaddition reactions. Theoretical studies and experimental findings are in well accord with each other.

4. CONCLUSIONS

The following main topics can be deduced from this study.

- Preparation and rearrangement of the 8-hydroxyquinoline derivatives were studied and there was not obtained any stable cycloadduct related with 8-hydroxyquinoline derivatives.

- Four types of pyridinium chlorides were prepared by mixing pyridine, 3 and 4-CN cyano substituted pyridines and 4-dimethylamino substituted pyridine with 2-chloro-N,N-dimethylacetamide at room temperatures moderate to higher yields.

- Four types of azomethine ylides were prepared from pyridinium chlorides *in situ* using triethylamine as a base in chloroform.

- These azomethine ylides were tested with various olefinic and acetylenic dipolaraphiles.

- The azomethine ylides, except 4-dimethylamino pyridine ylide, showed reactivity for 1,3-dipolar cycloaddition reactions with acetylenic dipolaraphiles dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate at room temperature.

- The azomethine ylides failed to give any cycloadduct with olefinic dipolaraphiles which are diphenyl acetylene, phenyl acetylene and vinyl acetate whether temperature were used or not without time-dependent.
- The unsubstituted and 4-cyano substituted pyridinium ylides showed symmetrical properties giving only one type of cycloadduct.
- The 3-cyano substituted ylide showed unsymmetrical properties giving two types of regioisomer based on the unsymmetrical reactive sites, but only one type of regioisomer could be obtained for characterization in very low yield.
- Six new carbamoyl substituted indolizines were synthesized via 1,3-dipolar cycloaddition reactions of azomethine ylides without using any catalyst such as K_2CO_3 for dehydrogenation forms of the cycloadducts.
- The structures of cycloadducts were characterized by means of IR, ^{1}H NMR and ^{13}C NMR spectra.

REFERENCES

[1] Narain R.P., 2008, Mechanisms in Advanced Organic Chemistry, New Age International (P) Ltd., New Delhi, p. 334

[2] Fleming, I., 1998, Pericyclic reactions, Oxford University, Oxford, p. 94

[3] Ansari, F.L., Qureshi, R., and Quereshi, M. L., Electrocyclic Reactions; From Fundamentals to Research, Wiley, Weinhem, 1999

[4] Carey F.A. and Sundberg R.J., 2007, Advanced Organic Chemistry, University of Virginia, Charlottesville, Virginia, p. 1212

[5] Huisgen R., 1968, Cycloadditions – Definition, Classification and Characterization., *Angew. Chem. Int. Ed. Engl*., 7, 321.

[6] Fernandez, I., Cossio, F. P., and Sierra, M. A., 2009, Dyotropic Reactions: Mechanisms and Synthetic Applications, *Chem. Rev*., 109, 6687-6711.

[7] Reetz, M. T., 1972, Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type I , *Angewandte Chemie International Edition in English* 11, 129 – 130.

[8] Reetz, M. T., 1972, Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type II, *Angewandte Chemie International Edition in English* 11, 130-131.

[9] Herndon, W. C., 1972, The Theory of Cycloaddition Reactions, *Chem. Rev*., 72, 157.

[10] Torshell, K. B. G. *Nitrile oxides, Nitrones and Nitronates in Organic Synthesis*; VCH, Weinheim, 1988

[11] Gothelf, K. V. , Jorgensen, K. A., 1998, Asymmetric 1,3-Dipolar Cycloaddition Reactions, *Chem. Rev.*, 98, 863.

[12] Huisgen, R., 1963, 1,3- Dipolar Cycloadditions Past and Future, *Angew. Chem., 75*, 604.

[13] Woodward, R. B., Hoffmann, R., 1968, The Conservation of Orbital Symmetry, *Acc. Chem. Res*., 1, 17.

[14] Woodward, R. B., Hoffmann, R., 1965, Stereochemistry of Electrocyclic reactions, *J. Am. Chem. Soc*., *87*, 395.

[15] Firestone, R. A., 1968, On the Mechanism of 1,3-Dipolar Cycloadditions, *J. Org. Chem*., 33, 2285-2290.

[16] Huisgen R., 1963,. *Chem. Int. Ed. Engl.*, 2, 565 (1963)

[17] Huisgen R., in 1,3-dipolar cycloaddition chemistry, Padwa, A. (Ed.), Wiley, New York, 1984; Vol.2, p. 83.

[18] Sustmann, R., 1971, A simple model for substituent effects in cycloaddition reactions. I. 1,3-dipolar cycloadditions, *Tetrahedron Lett.*, 12, 29, 2717.

[19] (a) Padwa, A., Weingarten, M. D., 1996, Cascade Processes of Metallo Carbenoids, *Chem. Rev., 96*, 223-269. (b) Mehta, G., Muthusamy, S., 2002, Tandem cyclization–cycloaddition reactions of rhodium generated carbenoids from α-diazo carbonyl compounds *Tetrahedron*, 58, 9477.

[20] Huisgen, R., 1984, In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley:New York, Vol. 1, p 1.

[21] Fukui, K., 1982, Role of Frontier Orbitals in Chemical Reactions, *J. Org. Chem*., 218, 747-754.

[22] Houk, K. N.; Yamaguchi, K., 1984, *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed., Vol. 2, p 407, Wiley: New York.

[23] Houk, K. N., Sims, J., Watts, C. R., Luskus, L. J., 1973, Origin of reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions., *J. Am. Chem.Soc.*, *95*, 7301.

[24] Sustmann, R., 1971, A simple model for substituent effects in cycloaddition reactions. I. 1,3-dipolar cycloadditions, *Tetrahedron Lett.*, 12, 29, 2717.

[25] Sustmann, R., 1974, Orbital energy control of cycloaddition reactivity, *Pure Appl. Chem.*, *40*, 569.

[26] Houk, K. N.,1979, Theoretical and experimental insights into cycloaddition reactions, *Top. Curr. Chem.*, 79, 1.

[27] Fukui, K., Yonezawa, T,. And Shingu, H., 1952, A Molecular Orbital Theory of Reactivity in Aromatic Hydrocarbons, *J .Chem. Phys*., 20, 722.

[28] Schoenebek, F., Ess, D. H., Jones, G. O., Houk, K. N., 2009, Reactivity and Regioselectivity in 1,3-Dipolar Cycloadditions of Azides to Strained Alkynes and Alkenes : A Computational Study, *J. Org. Chem*., 131 ,8121-8133.

[29] Fukui, K., 1971, Recognition of stereochemical paths by orbital interaction, Accounts Chem. Res., 4, 57.

[30] Salem, L., 1968, Intermolecular orbital theory of the interaction between conjugated systems. I. General Theory, *Jour. Of Am. Chem. Soc*., 90, 543-552.

[31] March, J., 1992, Adv. Org. Chem., p. 848.

[32] Dewar, M. J. S., Zoebisch, E. G., Healy, E. F., Stewart, J. J. P., 1985, AM1: A New General Purpose Quantum Mechanical Molecular Model, *J. Am. Chem. Soc*., 107, 3902-3909.

[33] Stewart, J. J. P., 1989, Optimization of parameters for semiemprical methods I. Method, *J. Comput. Chem.,* 10, 209-220.

[34] Sustmann, R., and Schubert, R., 1972, Substituents Effects in Diels-Alder Additions, *Angew. Chem. Int. Ed. Eng*., 11, 840.

[35] Fukui, K., Yonezawa, T., Nagata, C., And Shingu, H., 1954, Molecular Orbital Theory of Orientation in Atomatic, Heteroaromatic, and Other Conjugated Molecules, *J.Chem.Phys*., 22, 1433.

[36] Anh N.T., Lefour J.M, Eisestein O. And Hudson R.F., 1977, Simple prediction of cycloaddition orientation: I-Diels-alder reactions, *Tetrahedron*, 33, 523.

[37] Bestide J., Grandour E. N., and Rousseau O.H., 1972, Etude de I'orientation de la cycloaddition dipolaire 1,3, *Tetrahedron Letters*, 13, 4225-4228.

[38] Curtius, T., 1883, Ueber die Einwirkung von salpetriger Säure auf salzsauren Glycocoläther, *Ber. Dtsch. Chem. Ges.*, 16, 2230.

[39] Buchner, E., 1888, Einwirkung von Diazoessigäther auf die Aether ungesättigter Säuren, *Ber. Dtsch. Chem. Ges., 21*, 2637.

[40] Buchner, E., Fritsch, M., Papendieck, A., Witter, E. B., 1893, Ueber das Pyrazol. I. Allgemeines über Synthesen von Pyrazolderivaten mittelst Diazoessigester H., *Liebigs Ann.Chem.,* 273, 214.

[41] Huisgen R., Grashey R., and Steingruber E., *Tetrahedron Letters*, in the press; (1960)

[42] Longmire, J. M.; Wang, B.; Zhang, X., 2002, "Highly Enantioselective Ag(I)-catalyzed [3+2] Cycloadditin of Azomethine Ylides"; *J. Am. Chem. Soc., 124*, 13400

[43] Oderatoshi, Y., Cheng, W.; Fujitomi, S., Kasano, Y., Minakata, S., Komatsu, M., 2003, "Exo- and Enantioselective Cycloaddition of Azomethine Ylides Generated from *N*-Alkylidene Glycine Esters Using Chiral Phosphine-Copper Complexes"; *Org. Lett. 5*, 5043.

[44] Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jogensen, K. A., 2002, "Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides --- A Simple Approach to Optically Active Highly Functionalized Proline Derivatives"; *Angew. Chem. Int. Ed., 41*, 4236.

[45] Yan, X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.; Wu, Y., 2006, "A Highly Enantio- and Diastereoselective Cu-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with Nitroalkenes"; *Angew. Chem. Int. Ed.*, *45*, 1979.

[46] Najera, C.; Sansano, J. M., 2005, "Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides and Alkenes: The Direct Strategy to Prepare Enantioenriched Highly Substituted Proline Derivatives"; *Angew. Chem. Int. Ed.*, *44*, 6272.

[47] Houk, K. N.; Gonzalez, J.; Li, Y., 1995, Pericyclic Reaction Transition States: Passions and Punctilios, 1935-1995, *Acc. Chem. Res.*, *28*, 81.

[48] Najera, C.; Sansano, J. M., 2003, "Azomethine Ylides in Organic Synthesis"; *Curr. Org. Chem.*, *7*, 1105.

[49] Padwa, A., Ku, H., 1979, "Intramolecular Dipolar Cycloaddition Reactions with Azomethine Ylides"; *J. Org. Chem.*, *44*, 255.

[50] Vedejs, E., Grissom, J. W., 1986, "Oxazoline Route to Azomethine Ylides"; *J. Am. Chem. Soc.*, *108*, 6433.

[51] Orlek, B. S., Sammes, P. G., Weller, D. J. "Use of Steric Buttresses to Enhance Intramolecular Cycloaddition"; *J. Chem. Soc., Chem. Commun.* 1993, 1412.

[52] Hollingshead, R., *Oxine and its Derivatives*, Butterworth Scientific Publications, London, (1954).

[53] Philips, J. P., 1956, The Reactions of 8-Quinolinol, *Chem. Rev.*, 56, 271.

[54] Oettingen, W. F. V., 1933, *Therapeutic Agents of the Quinoline Group,* Chemical Catalog Company, New York, p. 33.

[55] Othmer, K., 1968, Encyclopedia of Chemical Technology, John Wiley & Sons, INC, New York, vol. 16, p. 874.

[56] Abd-Alla, M. A., Ahmed, A. H. N., El-Zohry, M. F., and Omar,F. A., *Proc. Indian Natl. Sci. Acad., part A,* 58, 261 (1992).

[57] Landquist, J. K., 1951, Synthetic antimalarials. Part XLVI. Some 4-dialkylaminoalkylaminoquinoline derivatives, *J. Chem. Soc.*, 1038.

[58] Butler, C. L., and Renfrew, A. G., 1938, Hydroxyalkyl Ethers of Basic Phenols. The Antipneumococcic Activity of Some 8-Quinolyl Ethers, *J. Am. Chem. Soc.,* 60, 1582.

[59] Gershon, H., McNeil, M, W., Parmegiani, R., and Godfrey, P. K., 1972, Antifungal activity of 7- and 5,7-substituted 8-quinolinols, *J. Med. Chem.*, 15, 987-989.

[60] Pastalka, K., Czech. CS 257,190, 1989. Appl. 86/9, 117,1986; 3pp.

[61] Urbanski, T., Slopek, S., and Venulet, J., 1951, Antitubercular activity of some 8-hydroxyquinoline derivatives, *Nature*, 168, 29.

[62] Yamato, M., Ando, J., Sakaki, K., Hashigaki, K., Wataya, Y., Tsukagoshi, S., Tashiro, T., and Tsuruo, T., 1992, Synthesis and antitumor activity of tropolone derivatives. 7. Bistropolones containing connecting methylene chains, *J. Med. Chem.*, 35, 267.

[63] Edgerton, W. H., and Burckhalter,J. H., 1952, Amebacidal Agents. II. 5-Acyl- and 5-Alkyl-7-dialkylaminomethyl-8-quinolinols, *J. Am. Chem. Soc.,* 74, 5209.

[64] Helton, A. W., and Kochan, W. J., 1967, Chemotherapeutic effects of cycloheximide thiosemicarbazone, phytoactin, and 8-quinolinol benzoate, with and without dimethyl sulfoxide and pruning, on the Cytospora cincta canker disease of prune trees, *Plant Dis. Rep.*, 51, 340.

[65] Ogata, A., and Kaneko, T., 1944, *J. Pharm. Soc. Japan,* 64, 246.

[66] Maggio, G. D., and Ciaceri, G., 1955, Rass. Clin. Terap. e . Sci. Affini, 54, 217.

[67] Hedley, M. E., Preston, A. F., Cross, D. J., and Butcher, J. A., 1979, Screening of Selected Agricultural and Industrial Chemicals as Wood Preservatives, *Int. Biodeterior. Bull.*, 15, 9.

[68] Shehata, F. A., Khalifa, S. M., El-Dessouky, I., Aly, H. F., 1993, Extraction of Pm(II) and Gd(III) by 8-Hydroxyquinoline and Sohe Related Amines in Chloroform from Nitrate Medium, *Solvent Extr. Ion Exch.*, 11, 861.

[69] Tennant, R. W., Margolin, B. H., Shelby, M. D., Zeiger, E., Haseman, J. K., Spalding, I., Caspary, W., Resnich, M., Stasiewicz, S., Anderson, B., Minor, R., 1987, Prediction of Chemical Carcinogenicity in Rodents from in vitro Genetic Toxicity Assays, *Science*, 236, 933.

[70] Shelby, M. D., Erexson, G. L., Hook, G. J., Tice, R. R., 1993, Evaluation of a three-exposure Mouse bone marrow micronucleus protocol: Results with 49 chemicals, *Environ. Mol. Mutagen*., 21, 160.

[71] Ewing, G. W., and Steck, E. F., 1946, Adsorption Spectra of Heterocyclic Compounds. I. Quinolinols ans Isoquinolinols, *J. Am. Chem. Soc.*, 68, 2181.

[72] Seguin, M., *Bull. Soc. Chim*., 566 (1946)

[73] Seguin, M., *Compt. Rend.*, 222, 952 (1946)

[74] Philips, J. P., Keown, R., Fernando, Q., 1953, The Reactions of Aldehydes and Aromatic Amines with 8-Quinolinol, *J. Am. Chem. Soc*., 69, 1952.

[75] Carlson, W. W., Cretcher, L. H., 1947, Hydroxyalkylation with Cyclic Alkylene Esters. I. Synthesis of Hydroxyethylapocupreine, *J. Am. Chem. Soc*., 69, 1952.

[76] Mander-Jones, B., Trikojus, *V. M.*, 1932, The Synthesis of Bases Allied to Coniine. Part 1. The Preparation and Pyrolysis of the Allyl Ethers of Heterocyclic Enols, *J. Proc. Roy. Soc. N. S. Wales*, 66, 300.

[77] Merchant, J. R., Pathare, P. M., 1987, *Indian J. Chem. Sect. B*, 26B, 786.

[78] Hassan, M. K., and Awad, J. M. A., 1991, *Bull. Fac. Sci.,* 20, 145.

[79] Gesto, C., Dela Cuesta, E., and Avendano, C., 1989, An Efficient Synthesis of 8-Methoxy-and 8-Hydroxy-1-methylcarbostyril, *Synth. Commun.,* 19, 3523.

[80] Dalimov, D. N., Karimov, D. T., Vaizburg, G. M., Abduvakhabov, A. A., Abdullaeva, L. K., Kamaev, F. G.,1988, Synthesis of number of derivatives of alkoloids and of nitrogen containing heterocycles and their anticholinesterase activities, *Khim. Prir. Soedin.,* 6, 825.

[81] Lukevics, E., Lapina, T., Segals, I., Augustane, I., and Verovskii, V. N., 1998, *Khim. Farm. Zh*., 22, 947.

[82] Buzzetti, F., Brasca, M. G., Crugnola, A., Fustinoni, S., Longo, A., Penco, S., Dalla, Z. P., and Comoglio, P. M., 1993, Cinnamamide analogs as inhibitors of protein tyrosine kinases, *Farmaco,* 48, 615.

[83] Ibatullin, Y. G., Fatkullin, R. M., Petrushina, T. F., Vilenchik, Y. M., Badovskaya, L. A., Lekonsteva, G. I., Gavrilova, S. P., Aleksandrova, G. A., and Leitis, L. Ya., *Khim. Geterotsikl. Soedin.,* 1308 (1992).

[84] Hedge, V., Hung, C. Y., Madhukar, P., Cunningham, R., Hopfner, T., and Thummel, R. P., 1993, Design of receptors for urea derivatives based on the pyrido [3,2-g]indole subunit, *J. Am. Chem. Soc*., 115, 872.

[85] Pfeiffer, M. J., and Hanna, S. B., 1993, Aminolysis of Activated Esters of Indole-3-acetic Acid in Acetonitrile, *J. Org. Chem*., 58, 735.

[86] Katritzky, A. R., and Rees, C. W., (Eds). *Comprehensive Heterocyclic Chemistry*, Vols 1-8. Pergamon Press, Oxford (1984)

[87] Katritzky, A. R., Feygelman, V., Masumarra, G., Barczynsky, A., and Szafran, M., 1990, Aromaticity as a Quantitative Concept. 2. Sixteen familiar five- and six-membered monocyclic heterocycles, *J. Prakt. Chem*., 332, 853-869.

[88] Simonyan, V. H., Zinin, A. I., Babaev, E. V., and Jug, K., 1998, Mechanism of cycloaddition to indolizines, *J. Phys. Org. Chem*., 11, 201-208.

[89] Katritzky, A. R., 1989, Advances in Heterocyclic Chemistry, Academic Press, San Diego, California, Vol. 45, 359.

[90] Bora, U., Saikia, A., Boruh, R. C., 2003, A Novel Microvawe-Mediated One-Pot Synthesis via a Three-Compenent Reaction, *Org. Lett*. 5, 435-438.

[91] Troll, T., Beckel, H., Lenther-Böhm, C., 1977, Electrochemical Synthesis of Substituted Indolizines; UV and fluorescence spectra, *Tetrahedron*, 53, 81-90.

[92] Przewloka, T., Chen, S., Xia, Z., Li, H., Zhang, S., Chimmanamada, D., Kostik, E., James, D., Koya, K., Sun, L., 2007, Application of DMF –methyl sulfate adduct in the regioselective synthesis of 3-acylated indolizines, *Tetrahedron Lett.*, 48, 5739-5742.

[93] Weide, T., Arve, L., Prinz, H., Waldmann, H., Kessler, H., 2006, 3-Substituted indolizine-1-carbonitrile derivatives as phosphatase inhibitors, *Bioorg. Med. Chem*. *Lett*., 16, 59-63.

[94] Kaloko Jr, J., Hayford, A., 2005, Direct Synthesis of Monofunctionalized Indolizine Derivatives Bearing Alkoxymethyl Substituents at C-3 and Their Benzofused Analogues, *Org. Lett*., 7, 4305-4308.

[95] Fang, X., Wu, Y., Deng, J., Wang, S., 2004, Synthesis of monofluorinated indolizines and their derivatives by the 1,3-Dipolar reaction of N-ylides with fluorinated vinyl tosylates, *Tetrahedron*, 60, 5487-5493.

[96] Millet, R., Domarkas, J., Rigo, B., Goossens, L., Goessens, J., Houssin, R., Henichart, J., 2002, Novel potent substance P and neurokinin A receptor antagonists. Conception, synthesis and bilogical evaluation of indolizine derivatives, *Bioorg. Med. Chem*., 10, 2905-2912.

[97] Teklu, S., Gundersan, L., Rise, F., Tilset, M., 2005, Electrochemical Studies of Biologically Active Indolizines, *Tetrahedron*., 61, 4643-4656.

[98] Gundersan, L., Malterud, K. E., Negussie, A. H., Rise, F., Teklu, S., Østby, O. B., 2003, Indolizines as Novel Potent Inhibitors of 15-Lipoxygenase, *Bioorg. Med. Chem*., 11, 5409-5415.

[99] Olejnikova, P., Birosova, L., Svorc, L., 2009, Antimicrobial and Antimutagenic Properties of Newly Synthesized Derivatives of Indolizine, *Sci. Pharm*., 77, 216.

[100] Gundersan, L. L., Negussie, A. H., Rise, F., Ostby, O. B., 2003, Antimycobacterial Activity of 1-Substituted Indolizines, *Arch. Pharm. Pharm. Med. Chem*., 336, 191-195.

[101] Harrell, W. B., and Doerge, R. F., 1967, Mannich bases from 2-phenylindolizines I. 3-alkyl-1-dialkylaminomethyl derivatives, *J. Pharm. Sci*., 56, 225.

[102] Gubin, J., Vogelear, H., Inion, H., Houben, C., Lucchetti, J., Mahaux, J., Rossels, G., Peiren, M., Clinet, M., Polster, P., and Chatelain, P., 1993, Novel heterocyclic analogs of the new potent class of calcium entry blockers: 1-[[4-(aminoalkoxy)phenyl]sulfonyl]indolizines, *J. Med. Chem*., 36, 1425.

[103] Weidner, C. H., Wadworth, D. H., Bender, S. L., and Beltman, D., 1989, Indolizines. 4. Dyes derived from oxoindolizinium ions and active metylene compounds, *J. Org. Chem*., 54, 3660.

[104] Dick, J. W., Gibson, W. K., Leaver, D., and Roff, J. E., 1981, Heterocyclic compounds with bridgehead nitrogen atoms. Part 9. Synthesis in the pyrrole [2,1,5-de]quinolizine ([2.3.3]cyclazine) series starting from indolizines, *J. Chem. Soc*., *Perkin Tran 1*., 3150.

[105] Katritzky, A. R., Qui, G., Yang, Baozhen., and He, H., 1999, Novel Syntheses of Indolizines and Pyrrolo[2,1-*a*]isoquinolines via Benzotriazole Methodology *J. Org. Chem*., 64, 7618.

[106] Scholtz, M., 1912, Die Einwirkung von Essigsaureanhydrid auf α-Picolin, *Ber.*, 45, 734.

[107] Scholtz, M., 1912, Über die Natur des Picolids und Pyrrocolins, *Ber*., 45, 1718.

[108] Scholtz, M., and Fraude, W., 1929, Über die Natur des Picolids und über die Einwirkung von Propionsaure-anhydrid auf α-Picolin, *Ber*., 62, 1068.

[109] Chichibabin, A. E., and Stepanow, F. N., 1929, Über das Picolid von M. Scholtz und über Acetylderivative des Indolizins und 2-methyl-indolizines, *Ber*., 62, 1068.

[110] Chichibabin, A. E., and Stepanow, S. N., 1929, *Zhur. Russ. Khim. Obshch*., 61, 1635.

[111] Chichibabin, A. E., 1927, *Zhur. Russ. Khim. Obshch*., 59, 477.

[112] Chichibabin, A. E., 1927, Tautomerie in der Pyridin-Reihe, *Ber*., 60, 1607.

[113] Borrows, E. T., and Holland, D. O., 1948, The Chemistry of the Pyrrocolines and the Octahydropyrrocolines, *Chem. Rev*., 42, 611.

[114] Mosby, W. L., in "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Part 1. Interscience, New York, 1961.

[115] Tamura, Y., Tsujimoto, N., Sumida, Y., and Ikeda, M., 1972, Intramolecular 1,5-cyclization of ylides : Synthesis of pyrazolo-[1,5-a]pyridines and indolizines *Tetrahedron* , 28, 21.

[116] Swinbourne, F. J., Hunt, J. H., Klinkert, G., 1979, *Adv. Heterocycl. Chem*., 23, 103.

[117] Broggini, G., Garanti, L., Molteni,G., Zecci, G., 1998, Synthesis of bis-(3,5)pyrazolophanes by sequential intermolecular-intramolecular nitrilimine cycloadditions *Tetrahedron*, 54, 2843-3852.

[118] Poissonnet, G., Theret-Bettiol, M. H., Dodd, R. H., 1996, Preparation and 1,3-Dipolar Cycloaddition Reactions of β-Carboline Azomethine Ylides: A Direct Entry into C-1- and/or C-2-Functionalized Indolizino[8,7-*b*]indole Derivatives *J. Org. Chem*., 61, 2273.

[119] (a) Tsuge, O., Kanemasa, S., Kuraoka, S., Takenaka, S., 1984, N-(Trimethylsilylmethyl)pyridinium Trifluoromethanesulfonates as Facile Precursors for Nonstabilized Pyridinium Methylides, *Chem. Lett.*, 13, 279.

[120] Shang, Y., Zhang, M., Yu, S., Ju, K., Wang, C., He, X., 2009, New route synthesis of indolizines via 1,3-dipolar cycloaddition of pyridiniums and alkynes, *Tetrahedron Lett*., 50, 6981-6984.

[121] Zugrăvescu, I., Petrovanu, M., N-Ylides Chemistry, McGraw-Hill Int., New York, 1976.

[122] Zugrăvescu, I., Petrovanu, M. Eds., Cicloaditii 3+2 dipolare, Academiei, Bucureşti, 1987.

[123] Georgescu, E., Georgescu, F., Danila, M. G., Filip, P. I., Drăghici, C., and Căproiu, M. T., 2002, New N-bridgehead heterocyclic compounds. I. Carbamoyl-substituted indolizines and benzoindolizines, *Arkivoc,* 2, 30-45.

[124] Harwood, L. M., Vickers, R. J., 2002, In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Padwa, A., Pearson, W. H., Eds., John&Sons, New York, p. 169-252.

[125] Pearson, W. H., Stoy, P., and Mi, Y., 2004, A Three Component, One Pot Synthesis of Indolizines and Relaed Heterocycles via the [3+2] Cycloaddition of Nonstabilized Azomethine Ylides, *J. Org. Chem*., 69, 1919-1939.

[126] Wang, B., Zhang, X., Li, J., Jiang, X., Hu, Y., Hu, H., 1999, Preparation of Indolizine-3-carboxamides and indolizine-3-carbonitriles by 1,3-dipolar cycloaddition of N-(cyanomethyl)pyridinium ylides to alkanes in the presence of tetrakispyridinecobalt(II) dichromate or manganese(IV) oxide, *J. Chem. Soc. Perkin Trans.1*, 1571-1575.

[127] Sarkunam, K., and Nallu, M., 2005, Synthesis of Some New Indolizines, *J. Heterocyclic Chem.*, 42, 5-11.

[128] Bayazıt, M. K., M.Sc. Thesis, 2005, 1,3-Dipolar Cycloaddition Reactions of Some Azomethine Imines and Azomethine Ylides, p. 105.

[129] Field, L. D., Sternhell, S., Kalman, J. R., 2002, Organic Structures From Spectra, John Wiley and Sons Ltd, West Succex, England, p. 369.

[130] Abraham, R. J., Fisher, J., Loftus, P., 1998, Introduction to NMR Spectroscopy, John Wiley&Sons Ltd., p. 271.

[131] Erdik, E., 2008, Organik Kimyada Spektroskopik Yöntemler, Gazi Kitapevi, Ankara, p. 531.

[132] Sustmann, R., and Thrill, H., 1972, Substituent Effects in 1,3-Dipolar Cycloadditions of Phenyl Azide, *Angew. Chem. Int. Ed. Engl*., 11, 838.

APPENDIX : IR , ^{1}NMR , ^{13}C NMR

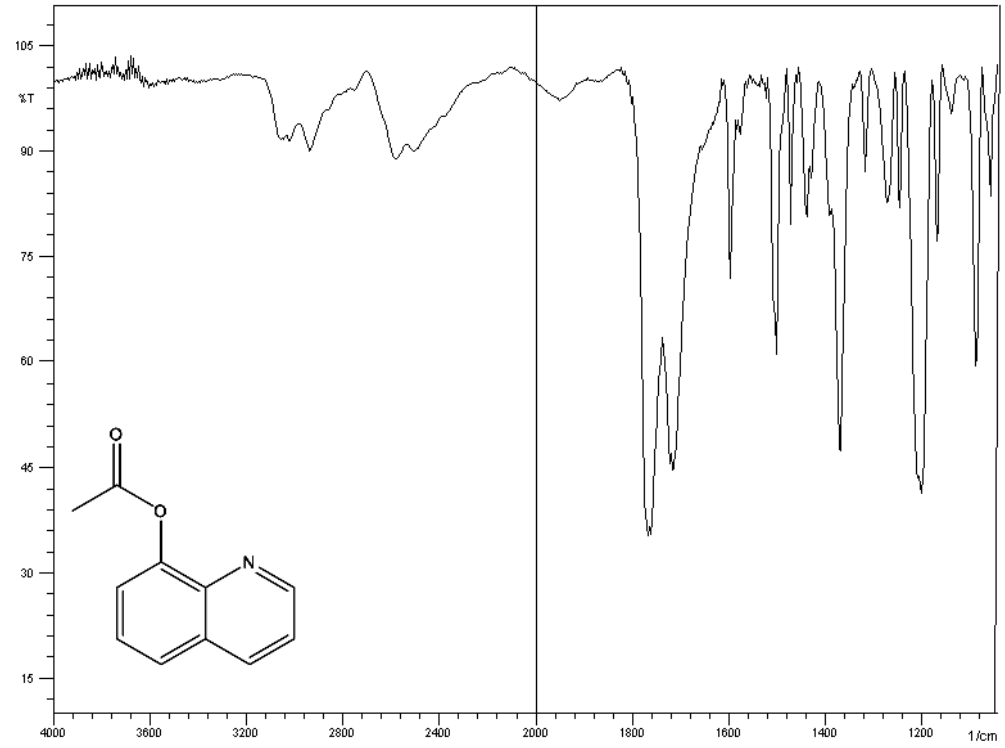


Figure 1. 43 The IR Spectrum of 2a

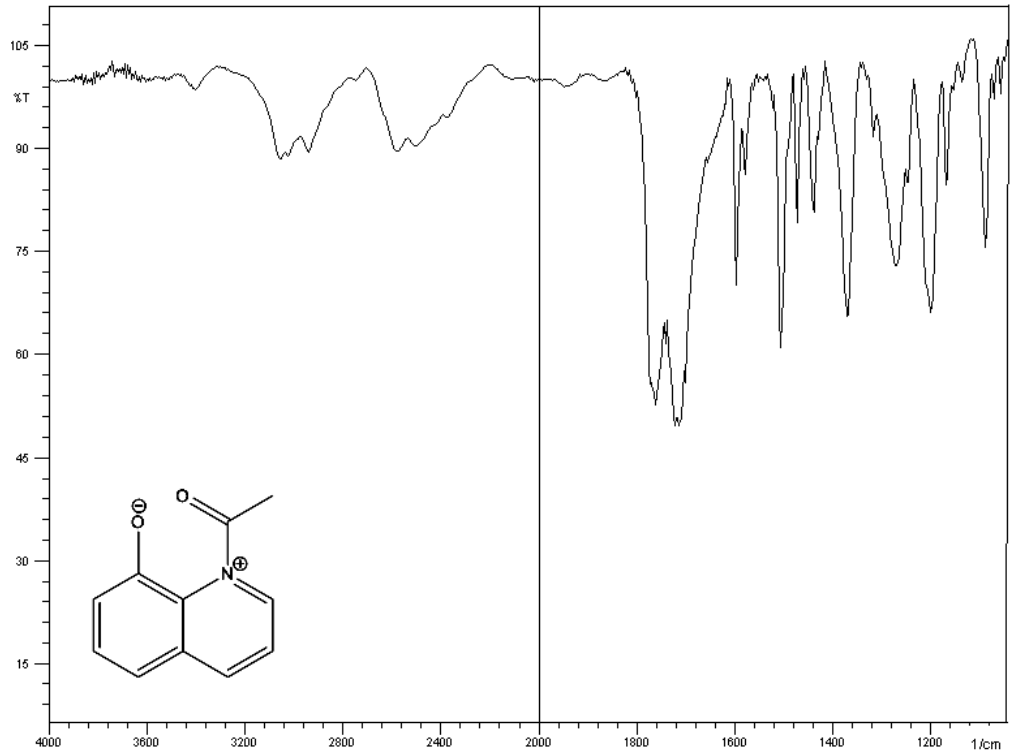


Figure 1. 44 The IR Spectrum of 2b

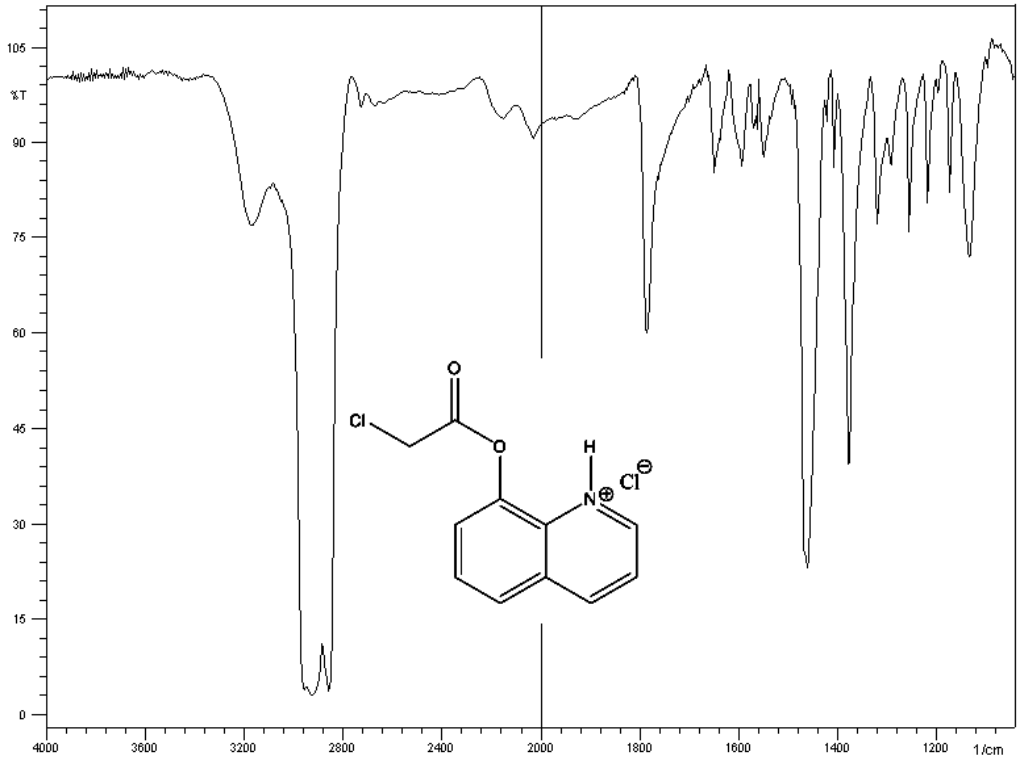


Figure 1. 45 The IR Spectrum of 2c

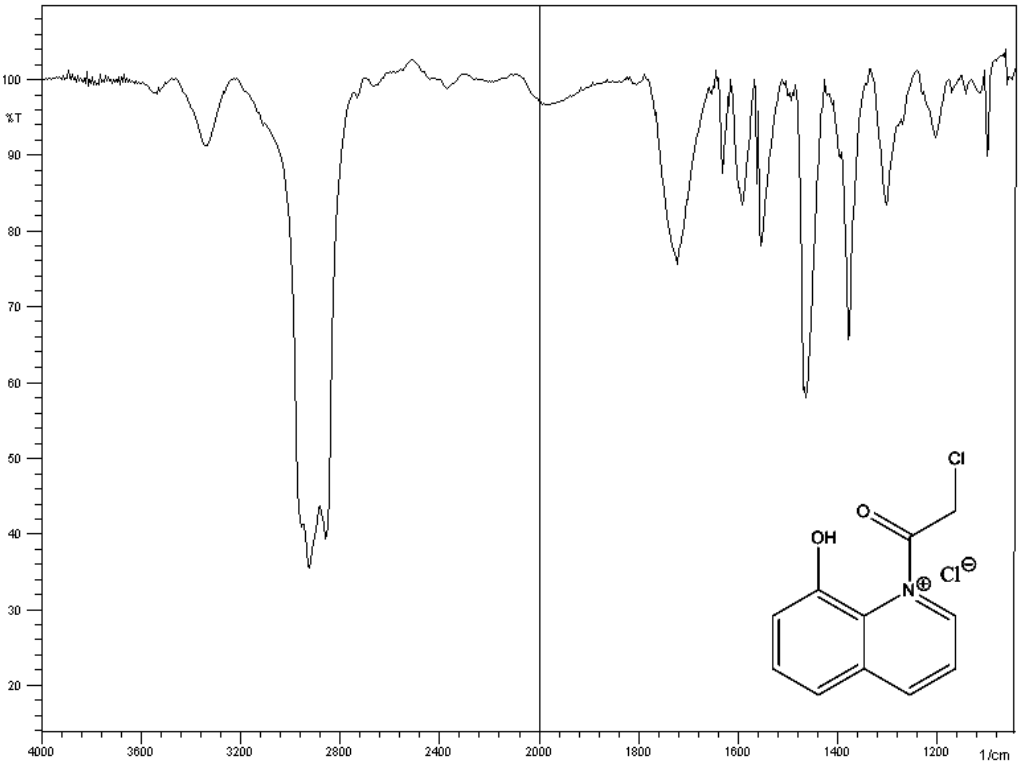


Figure 1. 46 The IR Spectrum of 2d

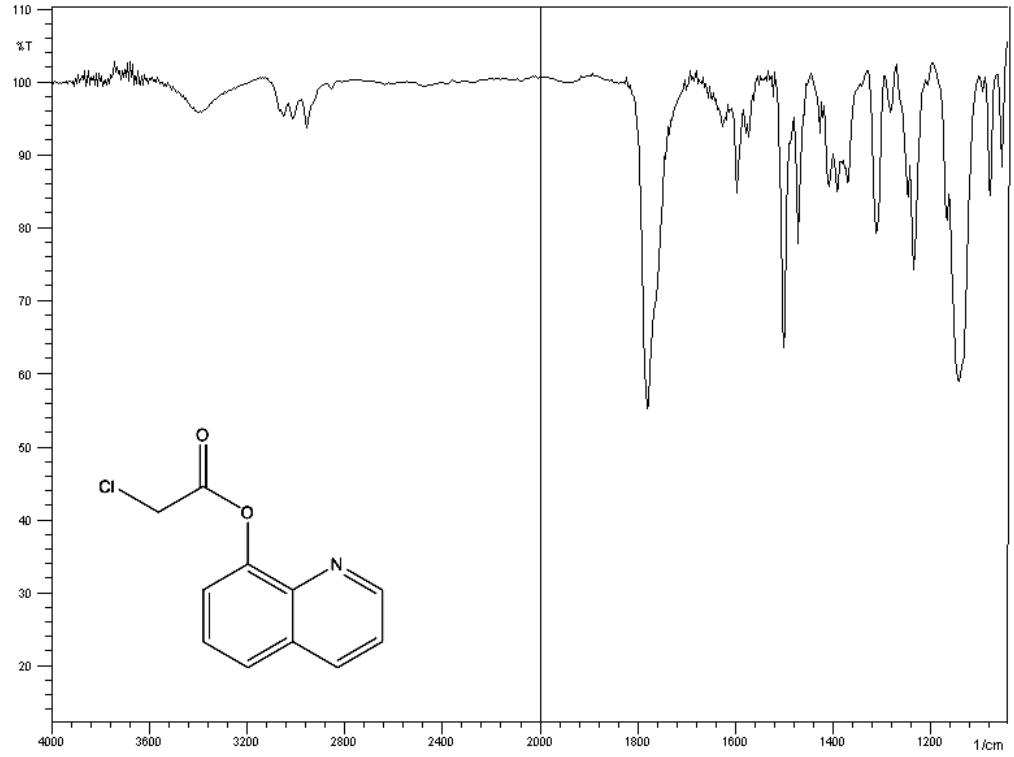


Figure 1. 47 The IR Spectrum of 2e

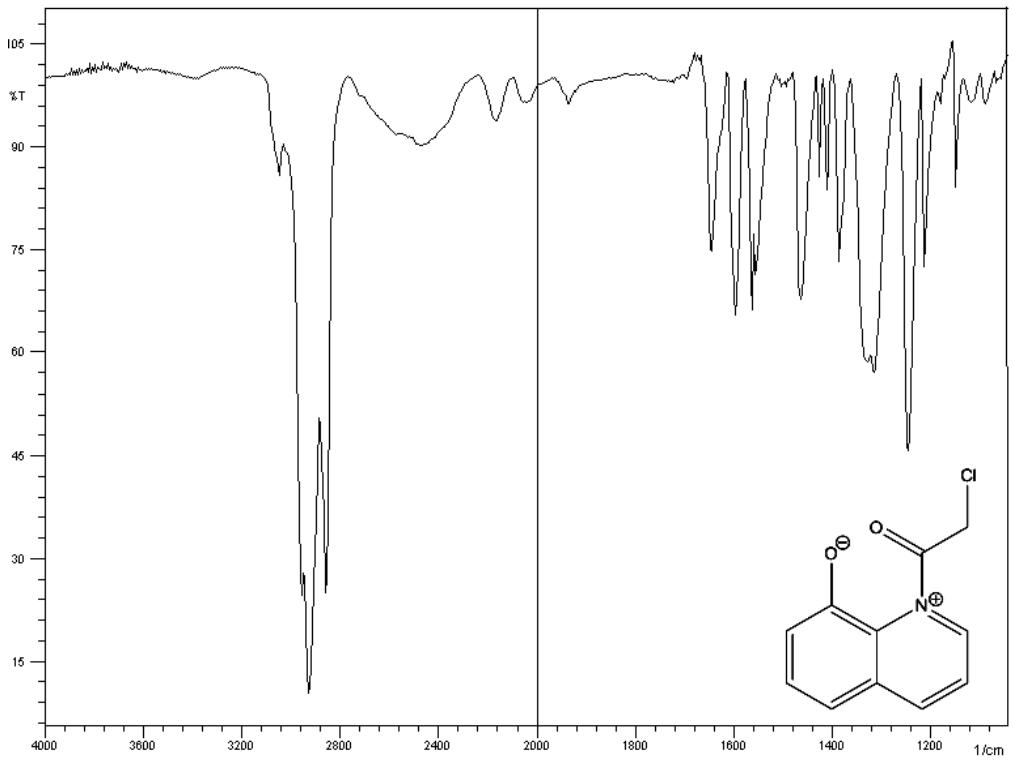


Figure 1. 48 The IR Spectrum of 2f

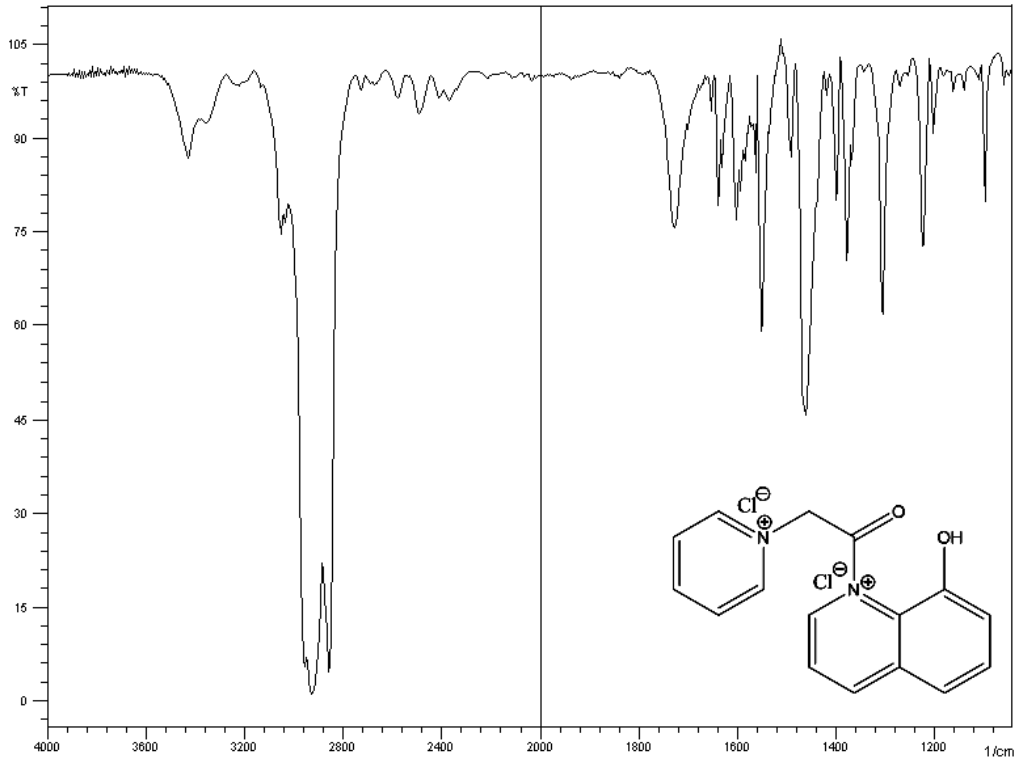


Figure 1. 49 The IR Spectrum of 2h

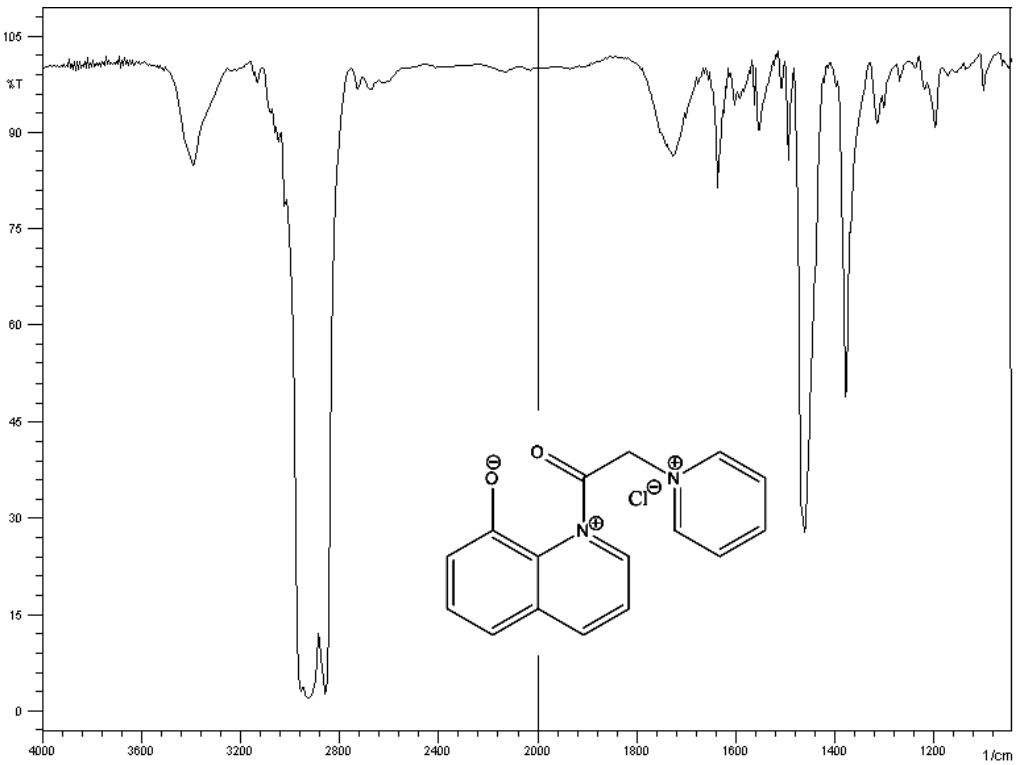


Figure 1. 50 The IR Spectrum of 2k

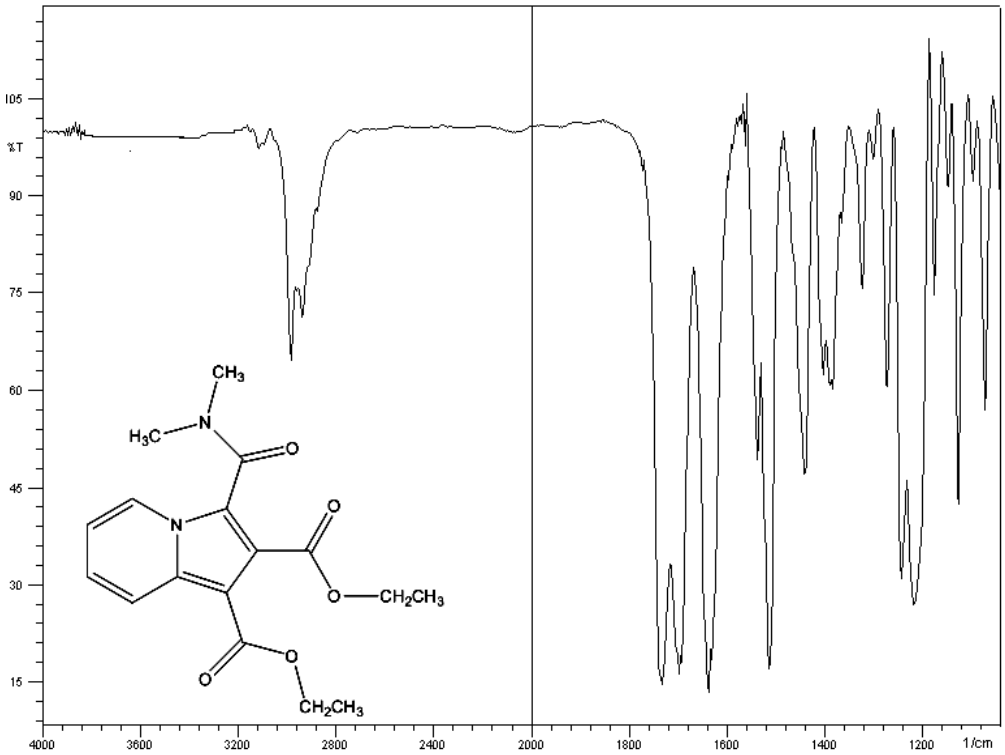


Figure 1. 51 The IR Spectrum of 5b

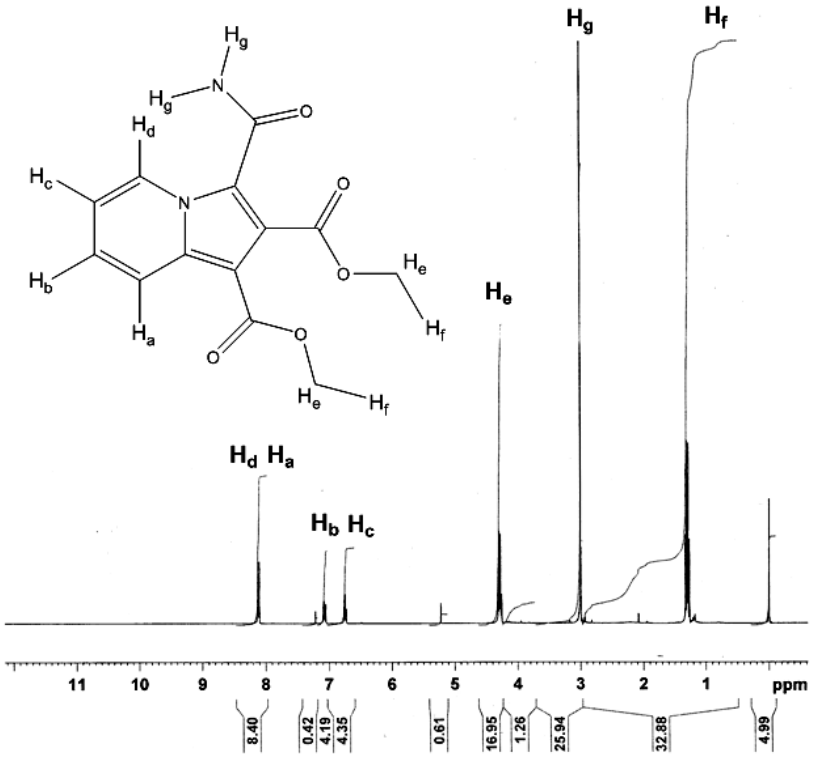


Figure 1. 52 The ^{1}H NMR Spectrum of 5b

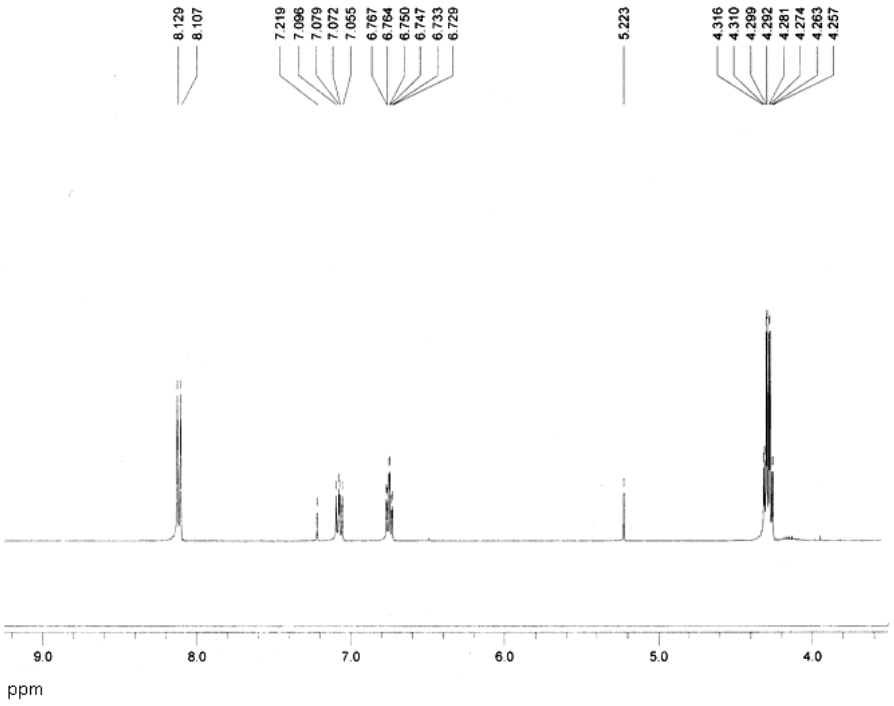


Figure 1. 53 Expanded (9.0-4.0 ppm) ^{1}H NMR Spectrum of 5b

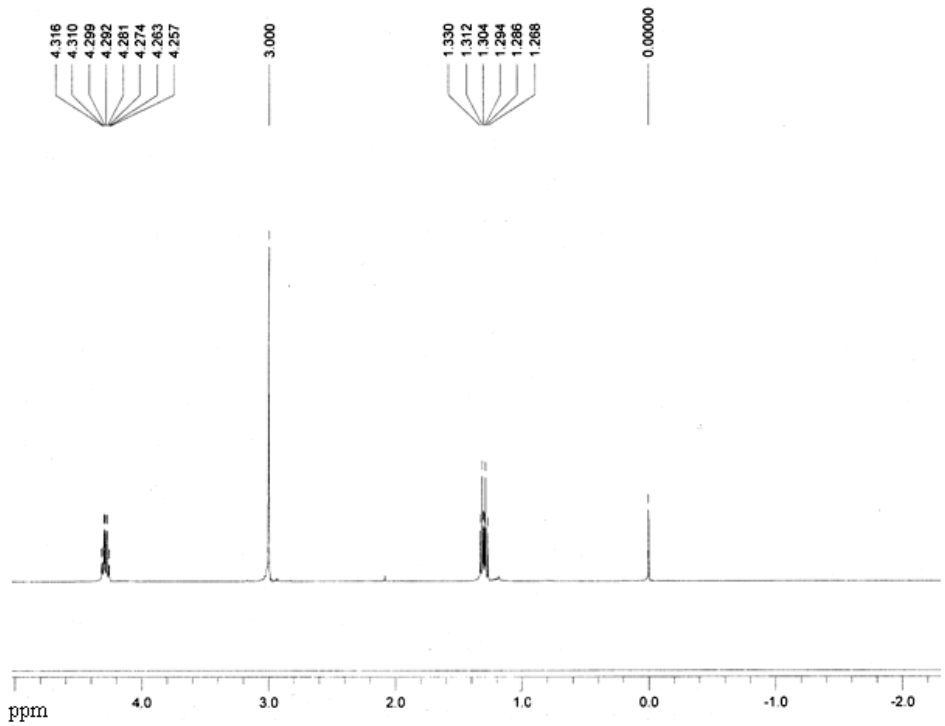


Figure 1. 54 Expanded (5.0-0.0 ppm) ^{1}H NMR Spectrum of 5b

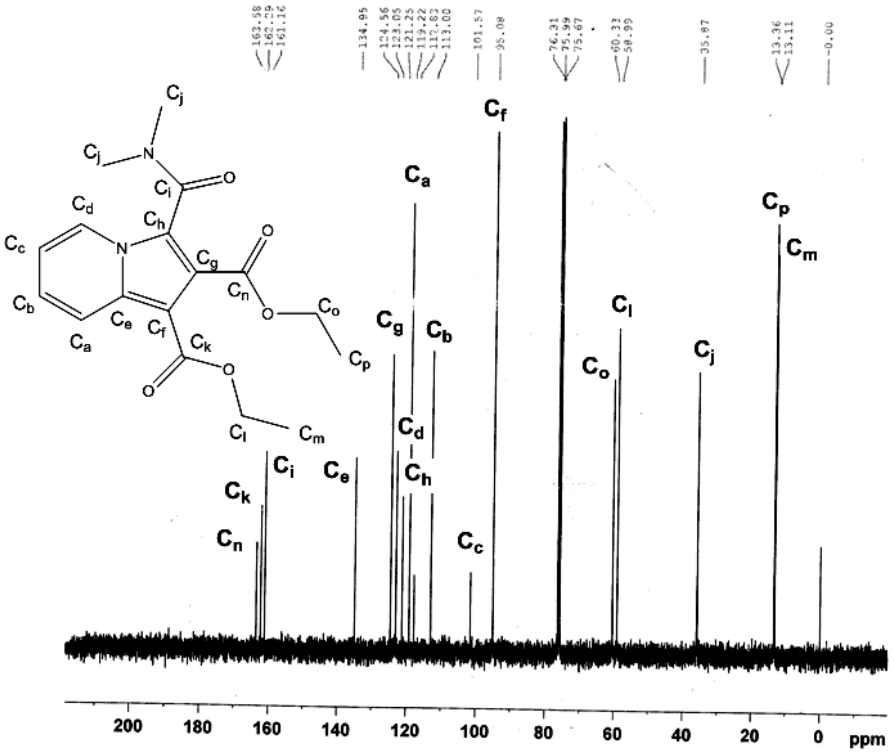


Figure 1. 55 The ^{13}C NMR Spectrum of 5b

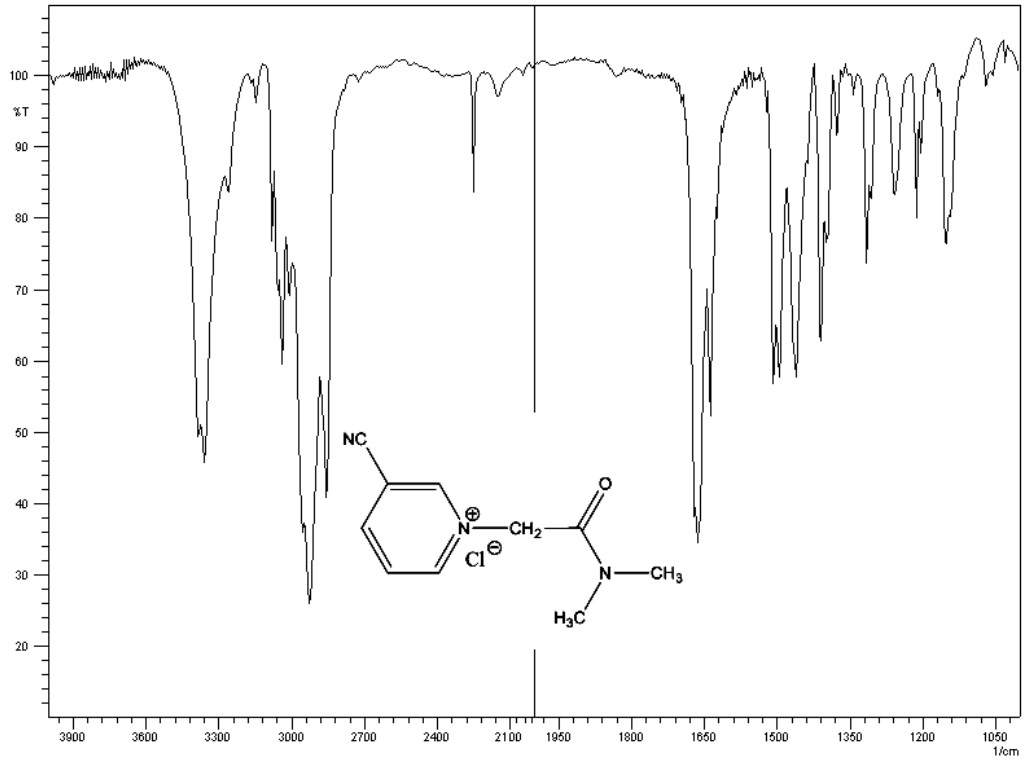


Figure 1. 56 The IR Spectrum of 3b

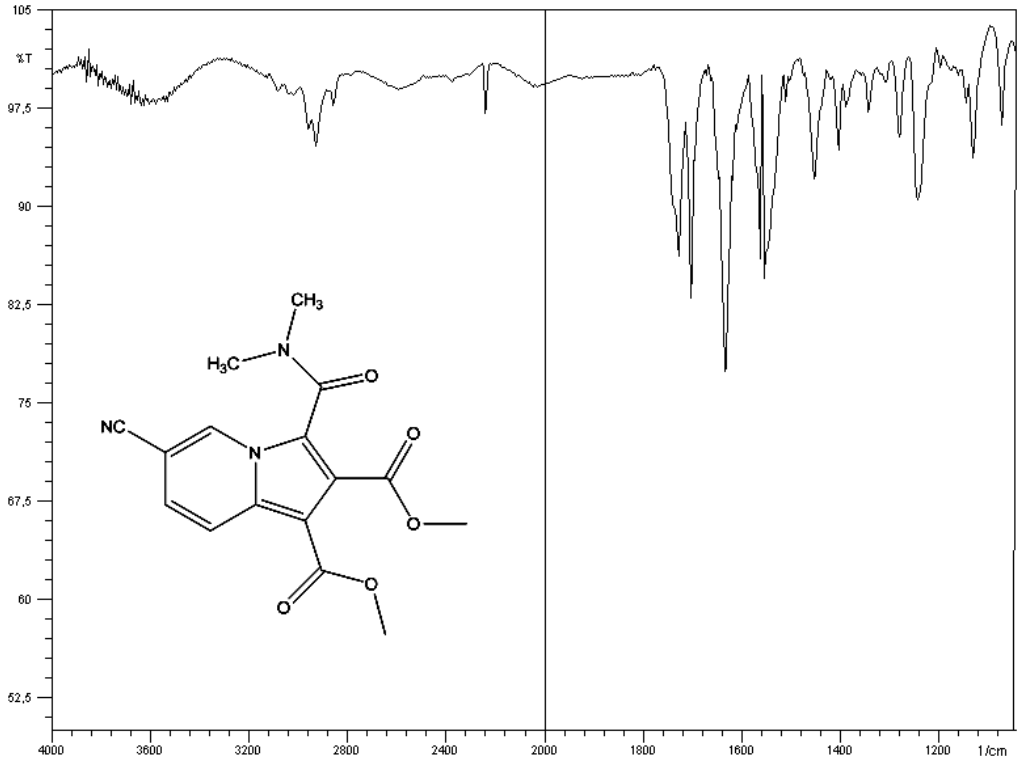


Figure 1. 57 The IR Spectrum of 5c

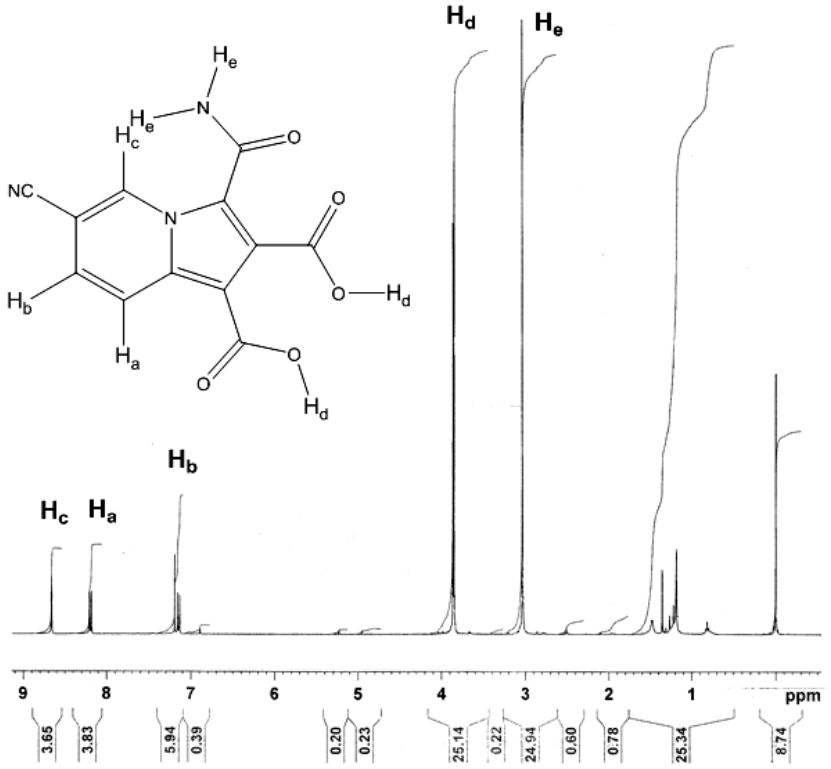


Figure 1. 58 The ^{1}H NMR Spectrum of 5c

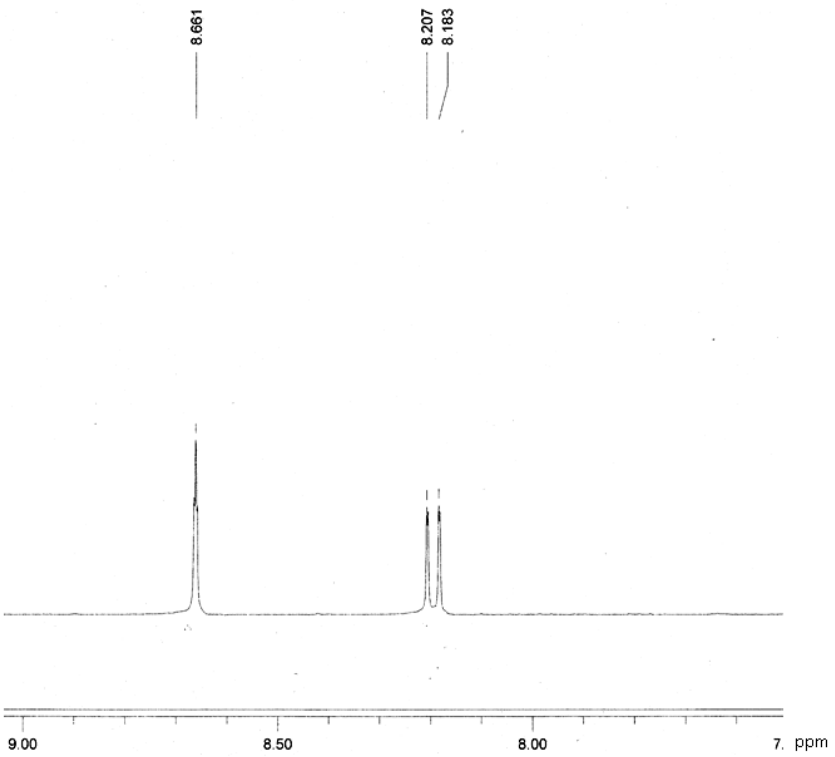


Figure 1. 59 Expanded (9.0-8.0 ppm) ^{1}H NMR Spectrum of 5c

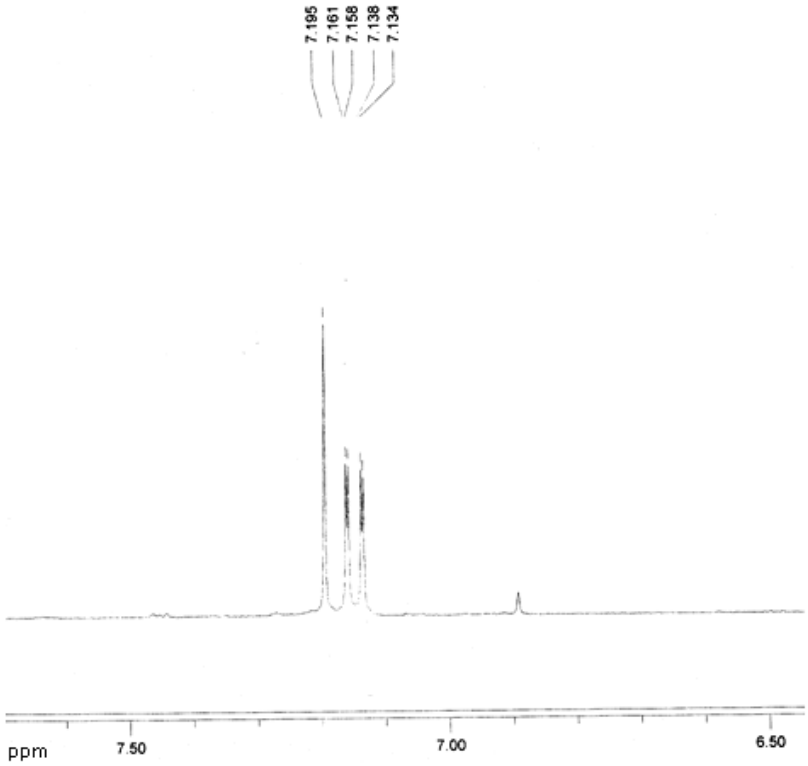


Figure 1. 60 Expanded (7.5-6.5 ppm) ^{1}H NMR Spectrum of 5c

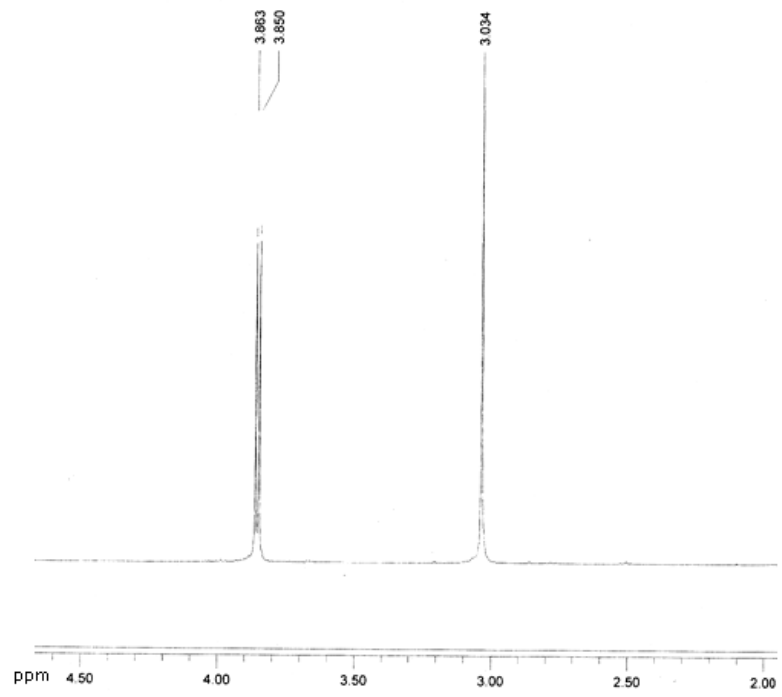


Figure 1. 61 Expanded (4.5-2.0 ppm) ^{1}H NMR Spectrum of 5c

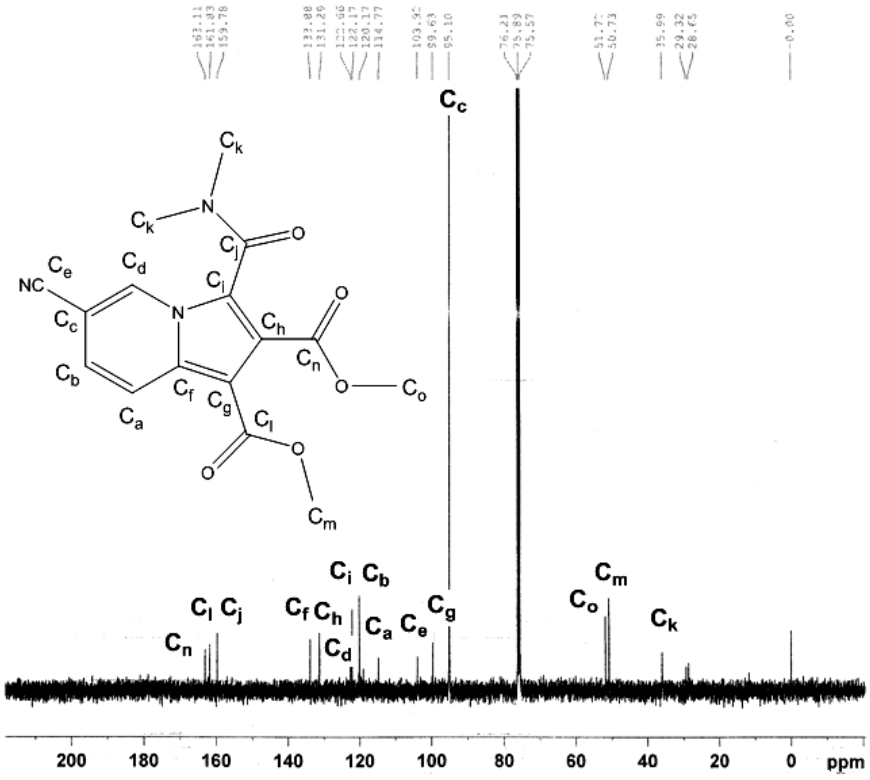


Figure 1. 62 The ^{13}C NMR Spectrum of 5c

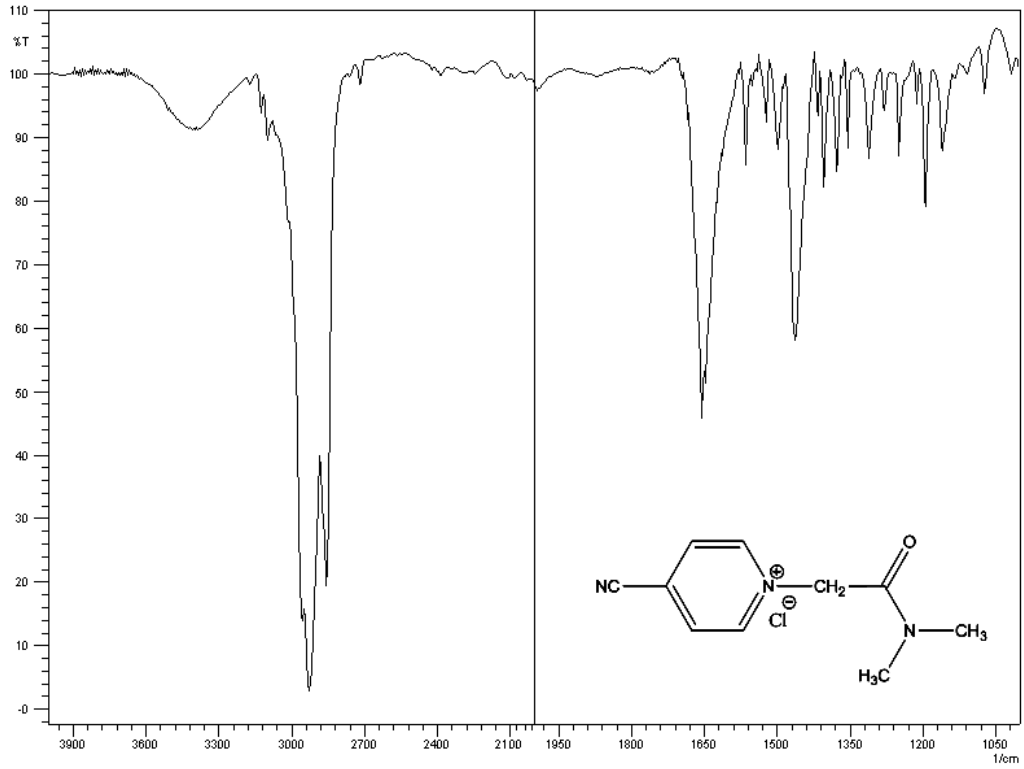


Figure 1. 63 The IR Spectrum of 3c

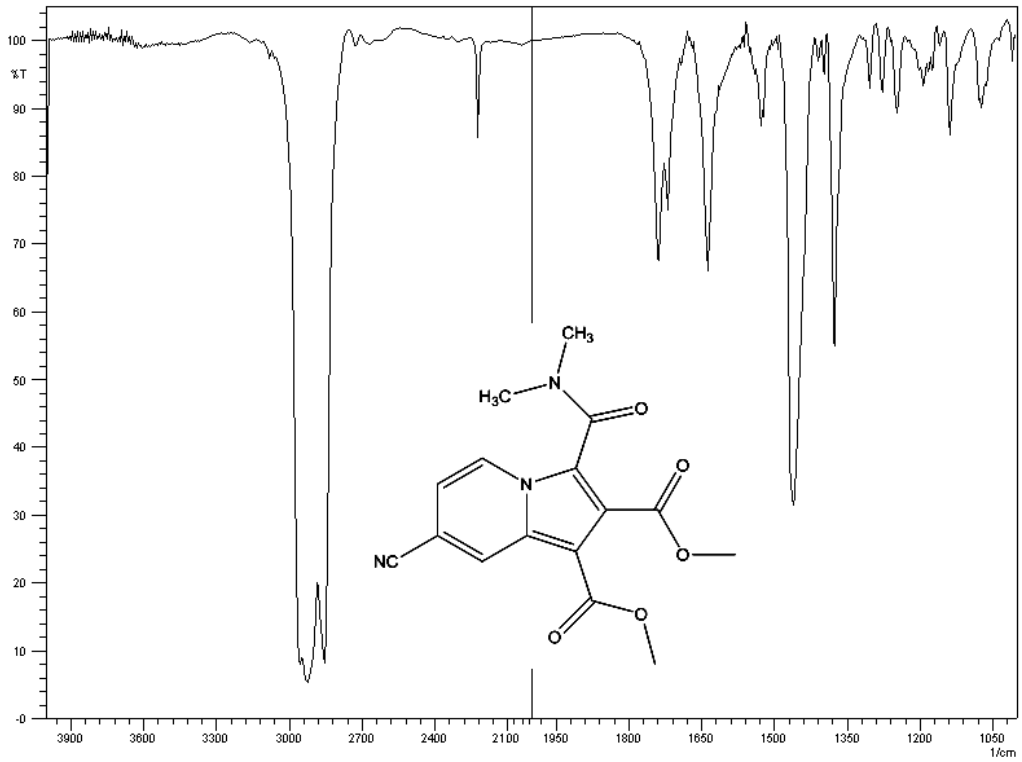


Figure 1. 64 The IR Spectrum of 5e

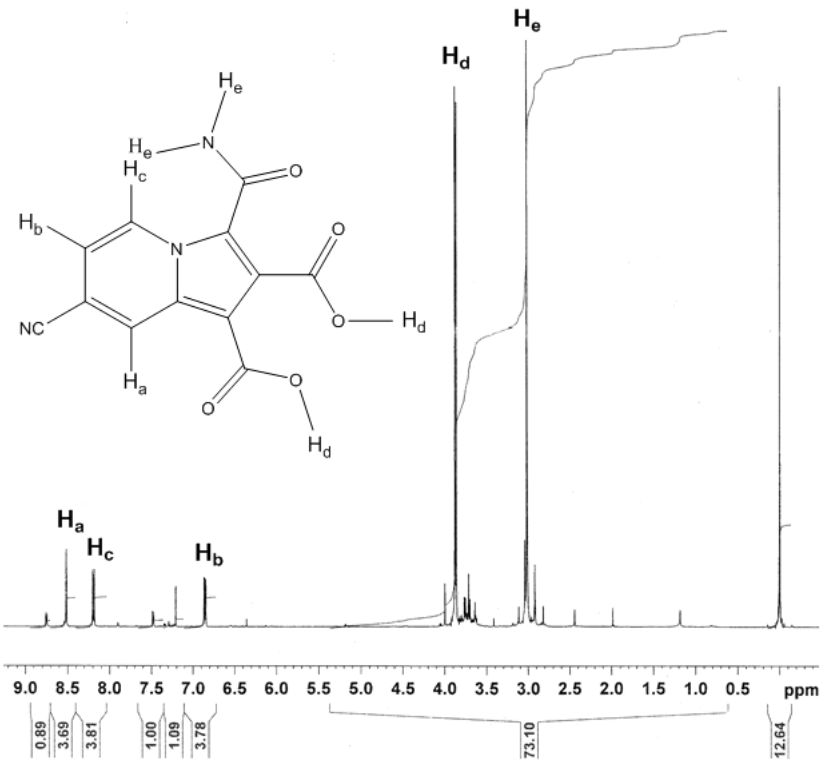


Figure 1. 65 The [1]H NMR Spectrum of 5e

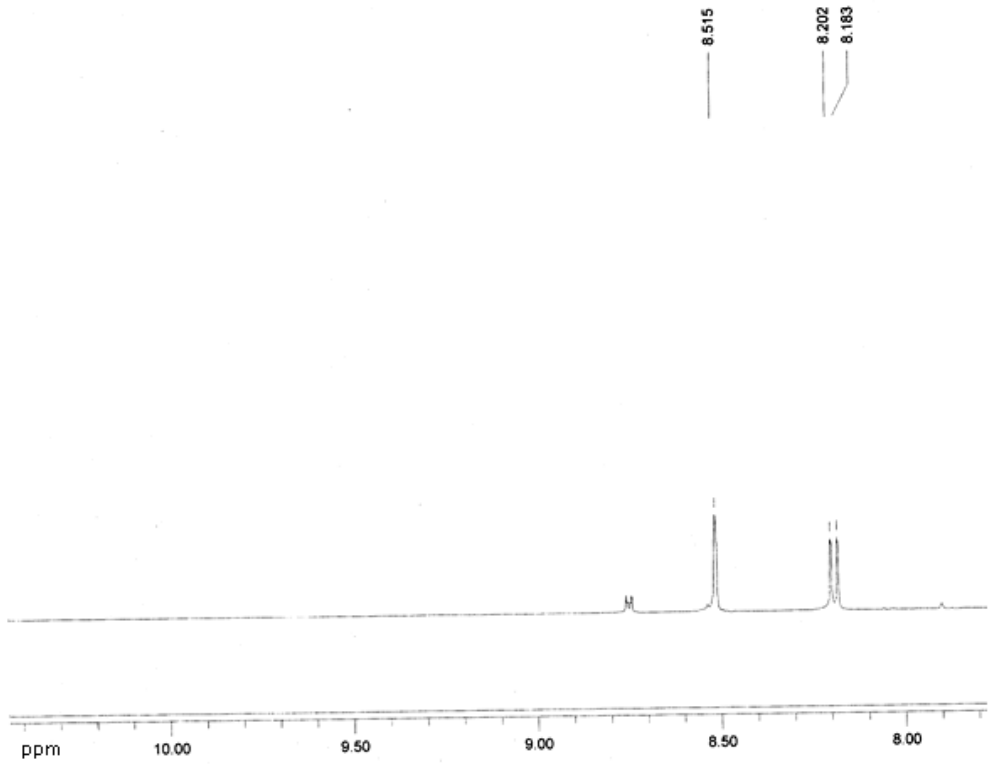


Figure 1. 66 Expanded (10.0-8.0 ppm) [1]H NMR Spectrum of 5e

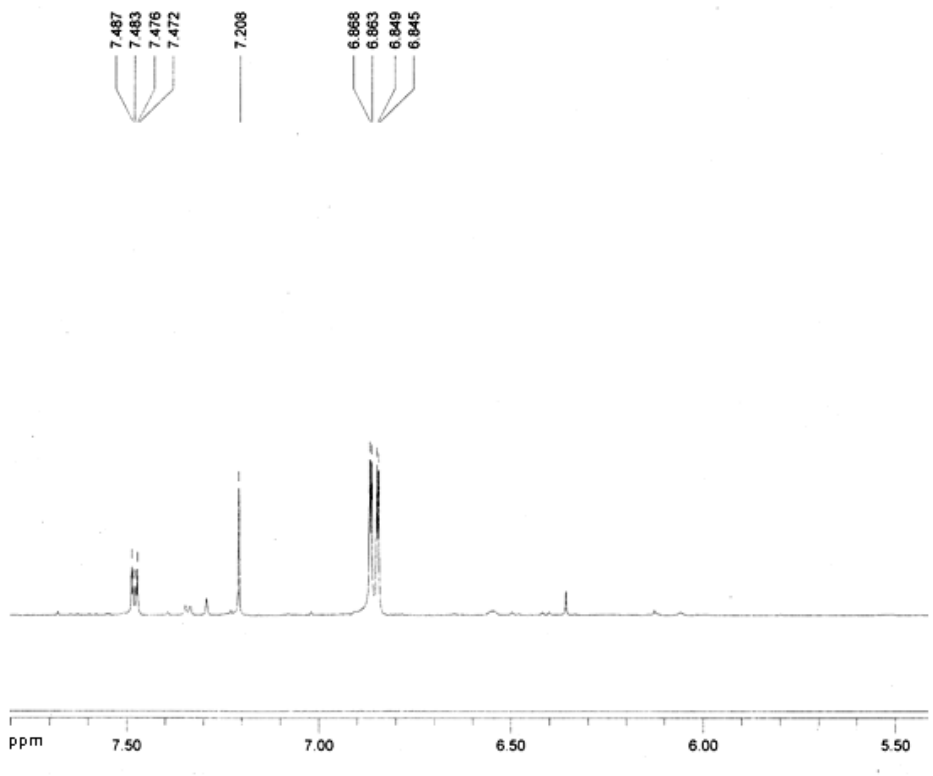


Figure 1. 67 Expanded (7.5-5.5 ppm) ^{1}H NMR Spectrum of 5e

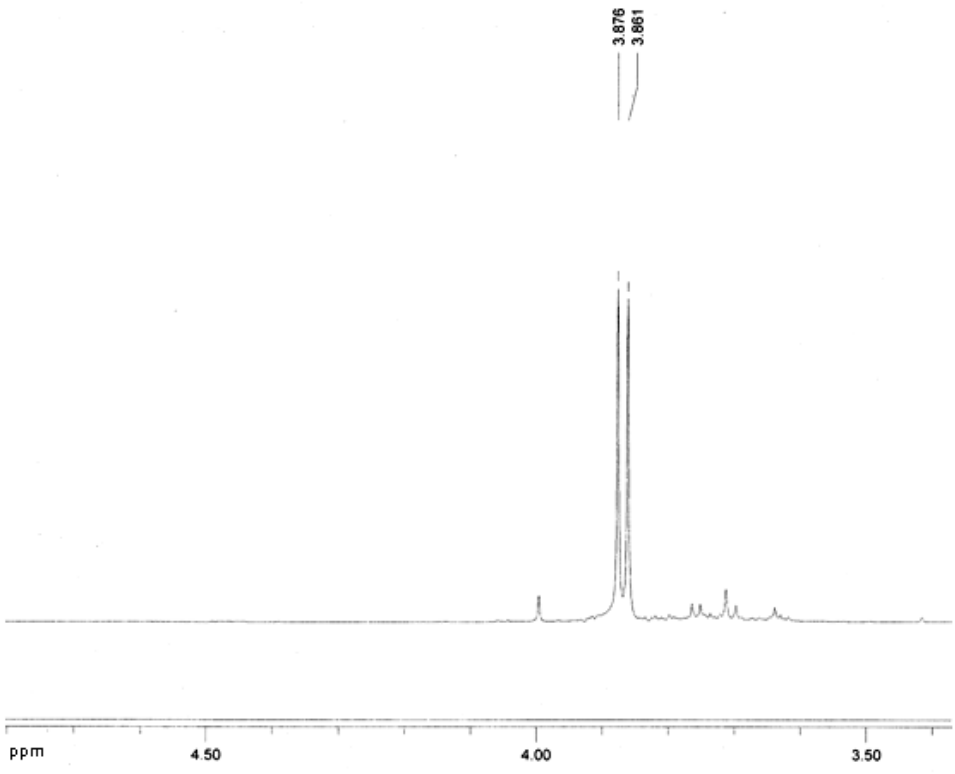


Figure 1. 68 Expanded (4.5-3.5 ppm) ^{1}H NMR Spectrum of 5e

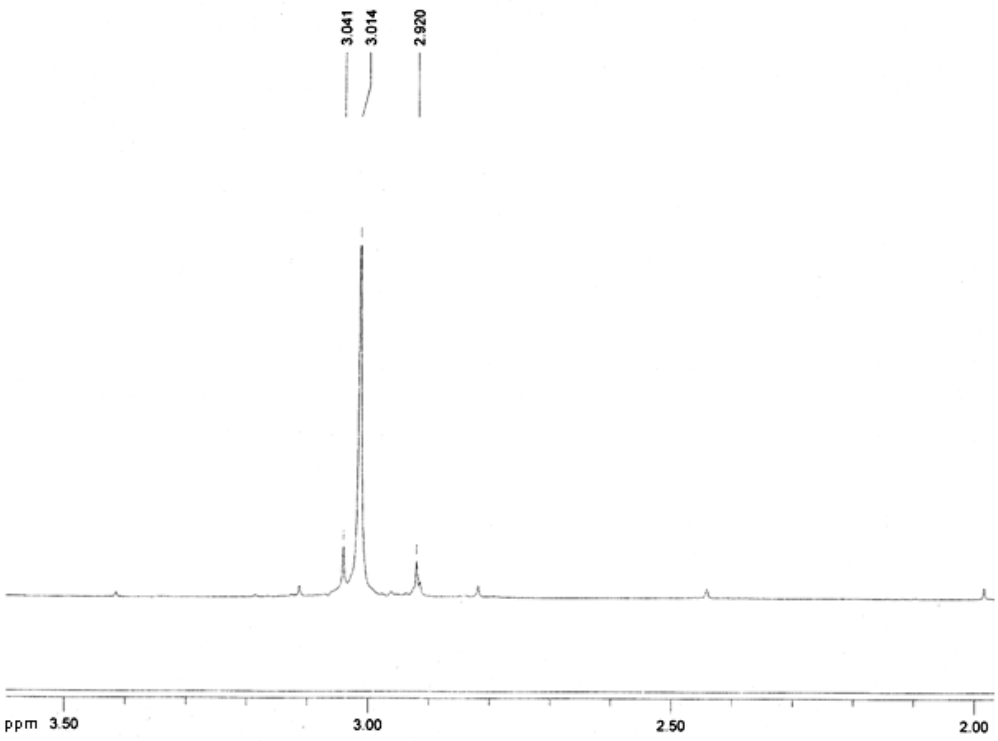


Figure 1. 69 Expanded (3.5-2.0 ppm) ^{1}H NMR Spectrum of 5e

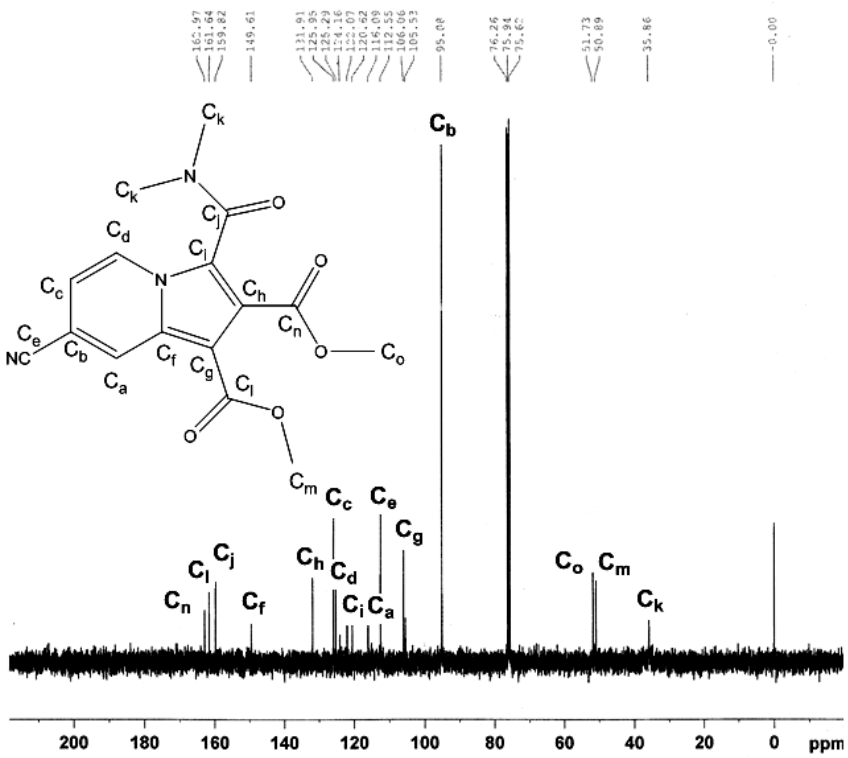


Figure 1. 70 The ^{13}C NMR Spectrum of 5e

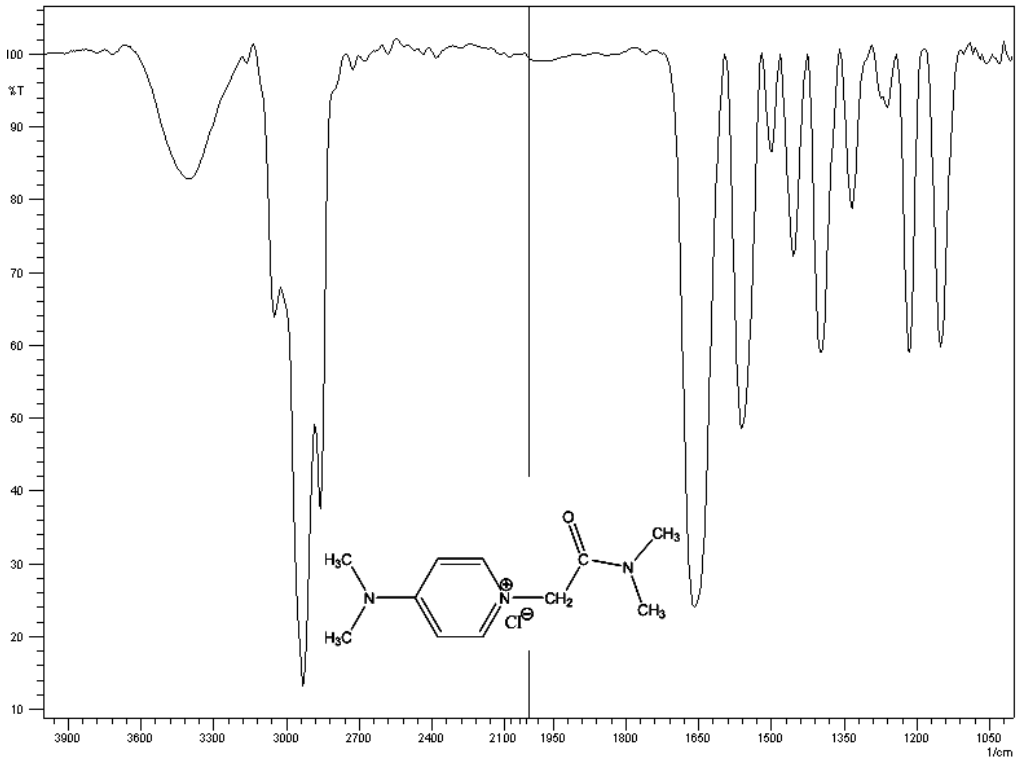


Figure 1. 71 The IR Spectrum of 3d