Further Exploration on Reactivity of Diazonium Salts with Selective Nucleophiles and Enolates

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Certificate of Examination

This is to certify that the dissertation titled "***Further Exploration on Reactivity of Diazonium Salts with Selective Nucleophiles and Enolates***" submitted by Mr. Devender Kumar (Reg. No. MS09049) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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Date:

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. Sugumar Venkataramani at the Indian Institute of Science Education and Research Mohali. This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

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In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. Sugumar Venkataramani

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Acknowledgement

Throughout the course of this project, I was accompanied and supported by many people. I would express my gratitude for all of them.

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Devender Kumar

To

My Kyra

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List of Schemes

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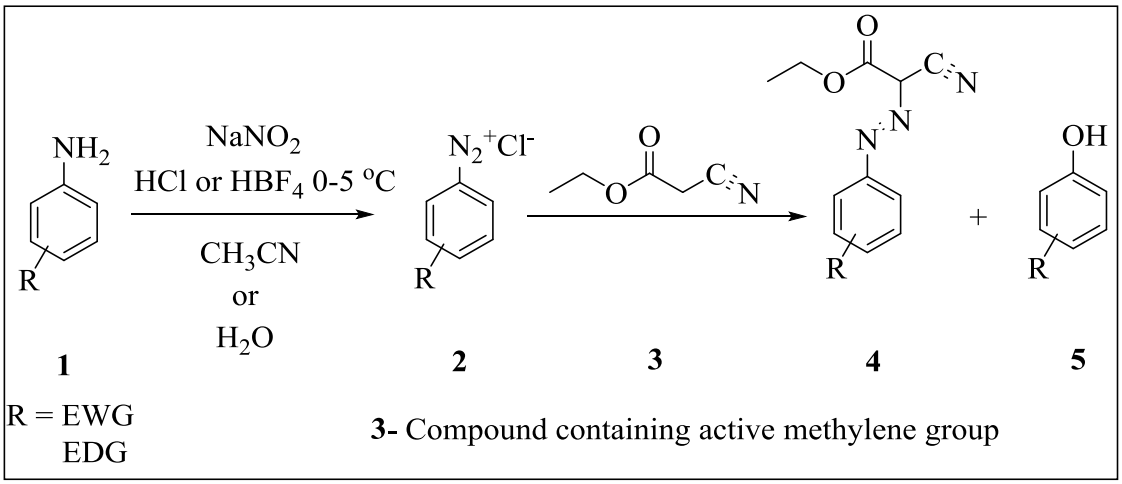
Abbreviations

CH_3COONa	:	Sodium acetate
DMSO	:	Dimethylsulfoxide
3-D	:	3-Dimensional
TLC	:	Thin Layer Chromatography
NMR	:	Nuclear Magnetic Resonance
H_2O	:	Water
I_2	:	Iodine
HCl	:	Hydrochloric acid
R.T	:	Room Temperature
CuBr	:	Copper bromide
O_2	:	Oxygen
NaOH	:	Sodium hydroxide
$SnCl_2$	:	Stannous chloride (Tin chloride)
DMF	:	Dimethylformamide
HRMS	:	High Resolution Mass Spectrometry
^{1}H-NMR	:	Proton NMR
^{13}C-NMR	:	Carbon-13 NMR
Na_2SO_4	:	Sodium sulphate
$NaNO_2$	:	Sodium nitrite
RBF	:	Round bottom flask
DCM	:	Dichloromethane

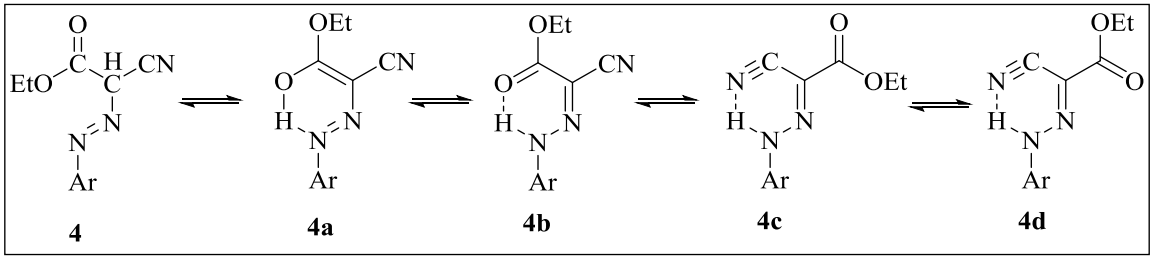
ACN	:	Acetonitrile
eq.	:	Equivalent(s)
hr	:	Hour(s)
FT-IR	:	Fourier Transform - Infrared Spectroscopy
CH_3CN	:	Acetonitrile
EWG	:	Electron withdrawing groups
EDG	:	Electron donating groups
Ar	:	Aryl
H_2SO_4	:	Sulfuric acid
HNO_3	:	Nitric acid
N_2O_3	:	Dinitrogen trioxide
HBF_4	:	Tetrafluoroboric acid

Abstract

A general method for the synthesis of azo derivatives of active methylene compounds through the *in situ* generation of arenediazonium salts followed by reacting them with a compound containing active methylene group has been developed. The advantages of these reactions are milder condition, cheaper starting material and simpler execution with high yields apart from many functionalization possibilities. Azo coupling of arenediazonium ion with aliphatic compounds are sensitive reaction so reaction conditions have been optimised by trying different conditions. Azo compound are robust photoswitchable molecules, which can be switched between *trans* and *cis* isomers. Due to this photoisomerization, azo molecules will get a significant geometrical change in their molecular structure. Due to the presence of two electron withdrawing groups, few different tautomeric structures are also possible for these systems. Through this work, synthesis, tautomerism and switching behavior have been studied in detail.



Scheme 1: General procedure for synthesis of azo compounds



Scheme 2: Tautomerization in azo-coupled compound

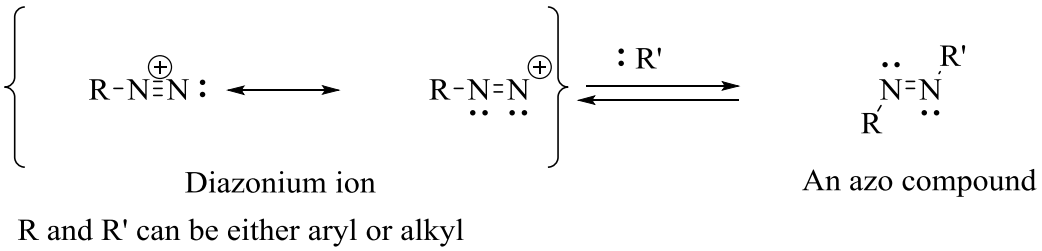
CHAPTER 1

INTRODUCTION

1.1 Azo Compounds

Azo compounds are the one of the important classes of derivatives, which has a general formula as (R-N=N-R) where R can be alkyl or aryl group. The azo functionality (-N=N-) is bound to aliphatic or aromatic units (-R). The nitrogen atoms of the azo bond (-N=N-)[1] are linked to a sp^2-hybridized carbon atom of the benzene ring. Diazonium salts, especially those where R is an aryl group, are important intermediates in the organic synthesis of azo dyes.

Kekula and Hidgh discovered coupling reactions of diazonium salts[2]. In all azo coupling, -N=N- functional group attached directly to aromatic rings. Even though coupling usually takes place with aromatic compounds, there are several aliphatic compounds capable of coupling with aryl diazonium ion. These aliphatic compounds have resonating substituents bestowing on the carbon atom an electron density enough for substitution by aryl diazonium ion. The first of these kind of the coupling of a diazonium salt with an activated aliphatic carbon atom was reported by Victor Meyer[3]. Due to resonance, in diazonium ions, the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. This coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice, it is found that the E-isomer predominates at equilibrium[3g].



Scheme 3: An azo compound

Azo compounds also bear very characteristic spectral properties. In spectrum, they are absorbing light in the visible region of the spectrum and are usually colored (yellow to

red) and are thus absorbing light in the visible region of the spectrum. Colored compound absorbs some, but not all wavelength of visible light. Functional groups that absorb light are called “Chromophores”. These are highly conjugated system containing several double bonds and one or more characteristic group such as azo, nitro and carbonyl. In azo compounds, an azo linkage serves as a part of its chromophores. Aliphatic azo compounds are inherently reactive molecules due to high nitrogen content and easy release of thermodynamically stable dinitrogen. Because of their high reactivity and nitrogen content, azo compounds are explosive compounds.

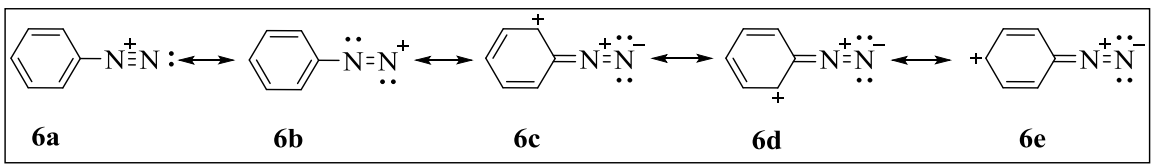
In 1858, Peter Griess reported first aromatic azo compounds[4]. In this work, Griess reported diazotization of *o*-aminophenol with nitrous acid (which itself was generated in situ by the reduction of nitric acid with arsenous acid). Azo compounds have general formula, ArN_2X and are broadly classified into two main groups:

1) Diazonium salts, $ArN_2^+X^-$,
2) Diazonium compounds, where atom or group X is covalently bound to the ArN_2 residue.

The high reactivity of arenediazonium ions is due to nitrogen, which is an exceptionally good leaving group [2]. Arenediazonium salts are normally prepared by the reaction of an aniline derivative with nitrous acid in the presence of a dilute aqueous mineral acid. Arenediazonium salts are relatively stable, whereas then aliphatic diazonium salts which decompose readily to give N_2 and a carbocation or undergoes deprotonation to form diazo compound, a key precursor for carbenes.

1.2 Diazonium Ion Structure.

Diazonium salts are an ionic compound in which positive charge is residing mainly on two nitrogen atoms On the basis of the concept of acids and bases the arenediazonium ion is Lewis acid and have following resonance structure.

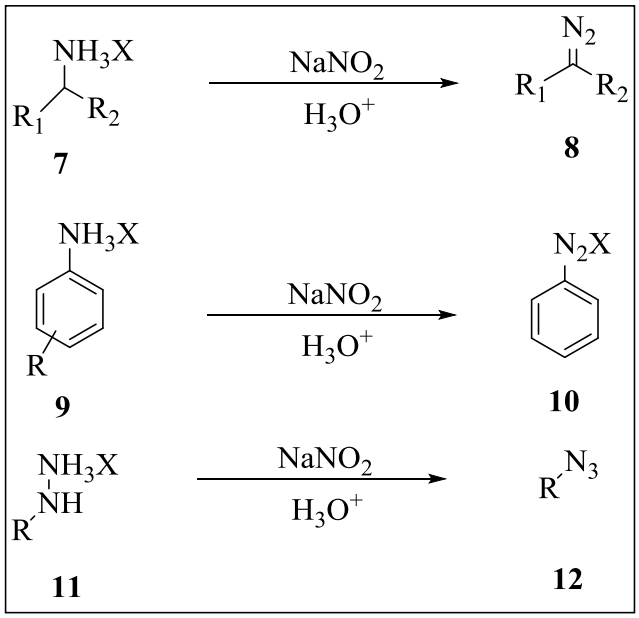


Scheme 4: Resonance structure of arenediazonium ion

Structure c-e explains the attack of a nucleophile on aromatic nucleus as a consequence of strong electron attraction by diazonium group.

1.3 Diazonium Salt Preparation (Diazotization).

The most common method for the preparation of diazonium compounds is the diazotization of the corresponding aniline derivatives. Generally, a variety of nitrosating agents, such as sodium nitrite in combination with any mineral acid are used for this purpose. This method is also used for diazotization of aliphatic amine and also synthesis of certain azides from the corresponding hydrazines[3]. Typically, an amine salt dissolved in aqueous acidic media at lower temperature (usually 0 °C or lower) followed by a slow addition of sodium nitrite. The active reagent, nitrous acid (HNO_2), is formed *in situ* and performs the diazotization. In aqueous medium reactant and product are exist wholly or partly in ionic form: as H^+X^-, $NaNO_2$ while the diazonium salts are practically completely ionized and the amine is in equilibrium with the corresponding ammonium ion, Ar—N^+H_3.



Scheme 5: Diazotization of aliphatic amines, aromatic anilines and hydrazines

Two equivalents of mineral acid are essential for smooth reaction. During the diazotization and at its completion, the solution should be distinctly acid. Because at higher pH the equilibrium ammoniumion $\rightleftharpoons$ amine is shifted in favor of the free base which, is less soluble in water. At low concentrations of hydrogen ions, the diazonium ion

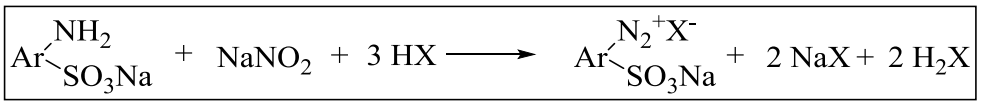
can react with the free base of unattacked amine to produce the triazene (diazoamino) compound.

Sodium nitrite should not be added in excess because diazotization is practically a quantitative reaction in contrast to ratio of amine to nitrite and in excess of nitrous acid stability of the arenediazonium cation get influence to the formation of an arene radical, nitrogen and nitrogen dioxide. That's why the concentration of nitrite is required to monitor in reaction. So we take some precaution as:

1) Determination of the content of diazotizable amine by titration with nitrite
2) Use of standard solutions of sodium nitrite.
3) Testing for the excess of nitrous acid at the end of the reaction. Starch-potassium iodide papers are best for this purpose as these turn blue instantaneously to indicate nitrite in acid solution.
4) Excess nitrite should be destroyed by adding sulfamic acid.

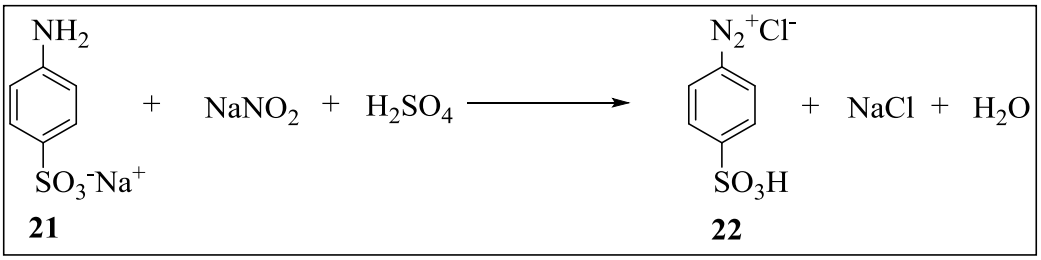
Diazotization is usually carried out at 0 °C because at low-temperature solubility of free nitrous acid is greater so there is less danger of escaping of the dangerous nitrous gases and most diazonium salts are stable at low temperature. Some diazonium salts are more stable so higher temperatures of diazotization may be used, such as 10-15 °C for sulfanilic acid. On a large scale, certain diazotizations are carried out at 30 °C, 40 °C and even higher; for example, 2-amino-5-benzamido-1, 1-diphenyl sulfone and its derivatives, or 3-aminodibenzofuran , are diazotized at 50 °C[3]. Some other methods are listed here:

Inverted method[3b]: Alkaline solutions of metallic nitrite and salt of sulfonated or carboxylated aryl amines are treated with an excess of cold mineral acid.



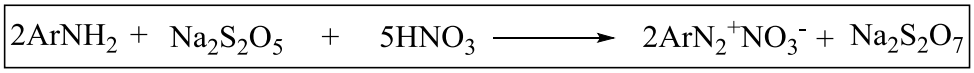
Scheme 6: General scheme for diazodization using inverted method

A solution of sodium nitrite and sodium sulphonate in water is slowly added into dilute sulphuric acid while stirring, diazonium compound can also be generated. This method is highly suitable for amino-acids, e.g. - sulphanilic, naphthionic, aminobenzoic acid and some weakly basic – amines.



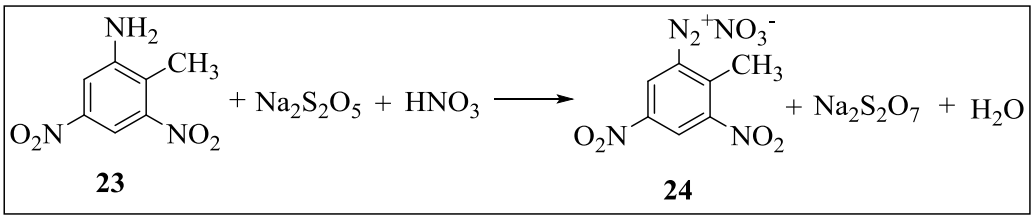
Scheme 7: Diazotization of sulphanilic acid

Witt method[3c]: In a solution of aryl amine with nitric acid, metabisulphite is added.



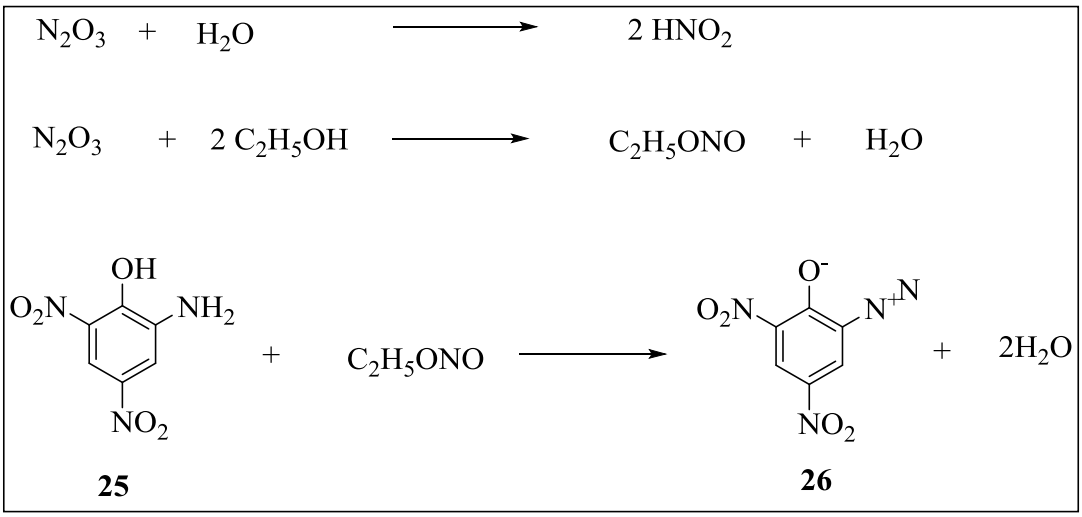
Scheme 8: General scheme for diazodization using Witt method

The dinitrotoluidine was treated with sodium metabisulphite and then nitric acid was added slowly to the mixture at 0 °C to get the diazonium compound.



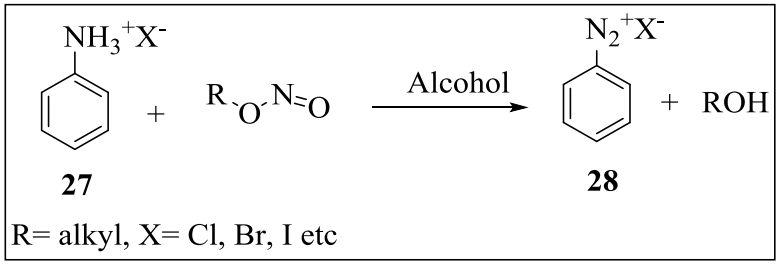
Scheme 9: Diazotization of 3,5-dinitro-*o*-toluidine

Griess method[3e]: In this method gaseous dinitrogen trioxide is being passed thorough the solution of arylamine in water or alcohol.



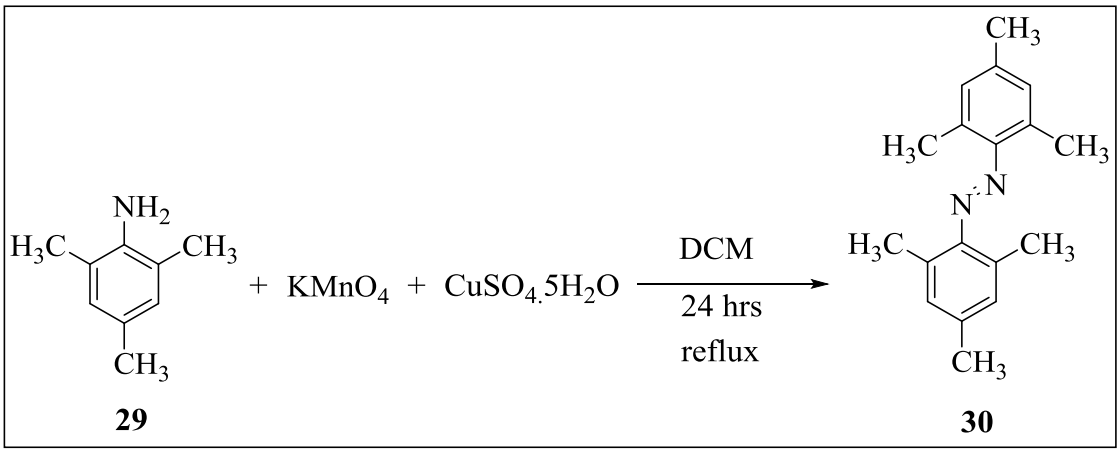
Scheme 10: Diazotization of picramic acid

Knoevenagel method[6]: In this method Knoevenagel modified the original method of Griess by replacing the nitrous acid gases by the more accurately controllable alkyl nitrites as the source of nitrous acid. In this method alkyl nitrite or ester of nitrous acid is added to a solution of salts of aryl amine in water or any inert solvent. The diazonium salt of their respective amines can also be prepared under anhydrous conditions using isoamyl nitrite in organic solvents.



Scheme 11: Preparation of diazonium compound using Knoevenagel's method

Other general methods for the preparation of azo compounds[3f]: Oxidation reactions for the synthesis of azo compound these reactions are carried out in the presence of oxidizing agents like a mercuric oxide, mercuric acetate, nitrogen trioxide.



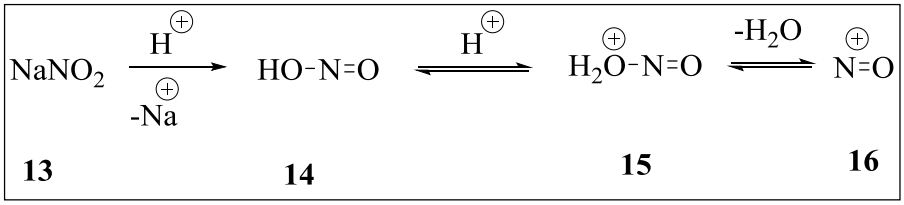
Scheme 12: Preparation of 1,2-bis(2,4,6-trimethylphenyl)diazene by oxidative method

Reduction reactions for synthesis of azo compound in this reaction hydroxylamine, acetyl chloride, like reducing agent are being used [6].

1.4 Mechanism[14]

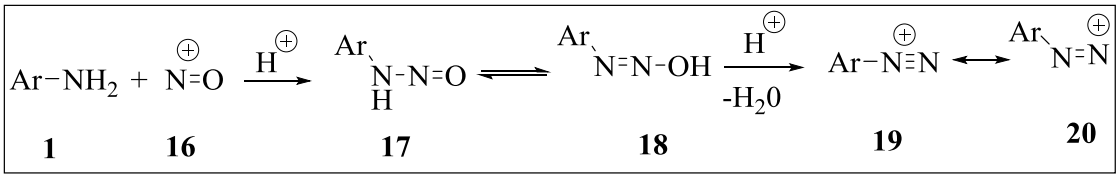
Firstly the nitrosating agent NO^+ liberates in situ from sodium nitrite. This is done using an acid. The nitrous acid is formed at first and further protonation and water elimination

provides the nitrosating agent.



Scheme 13: Formation of the nitrosating agent NO^+ (**16**)

Electrophilic nitrosation of the amino group of a primary aromatic amine is done by $N{=}O^+$. The first intermediate is the formation of the N-nitroso derivative, a tautomer of the diazohydroxide. A second protonation a water elimination afford the Diazonium salt which is stabilized by resonance.



Scheme 14: Formation of a diazonium salt (**20**) from an aniline derivative (**1**) and the nitrosonium ion (**16**)

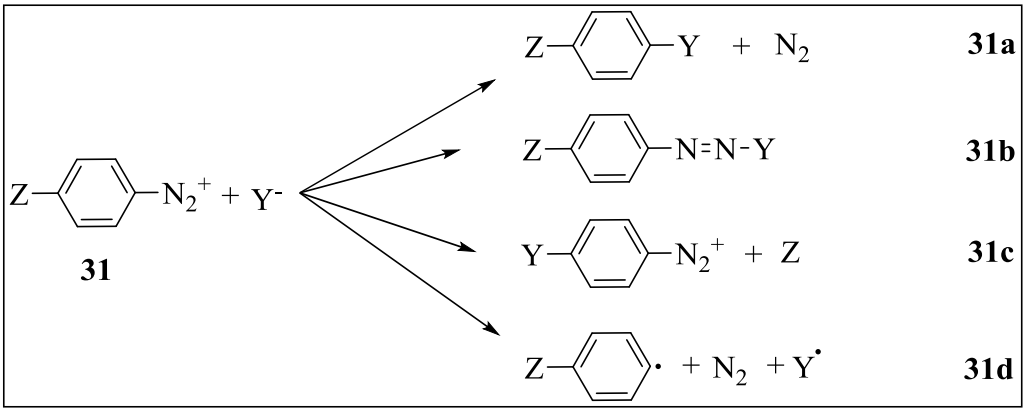
Diazonium salts are weak electrophiles and react with electron-rich species to give azo compounds.

1.5 Reaction of arenediazonium salts

The reactions of arenediazonium ion have been studied extensively[14]. The main type of arenediazonium ion reactions are summarized in scheme these include:

a) Replacement of nitrogen by a nucleophile (via phenyl cation, SN_2, benzyne formation)……..**(31a)**
b) Reactions of a nucleophile at the terminal nitrogen…….(**31b**)
c) Nucleophilic aromatic displacements activated by the strong electron withdrawing diazonium group…..(**31c**)
d) Free radical reactions (where Y may be a metal or other electron donor)…..(**31d**)

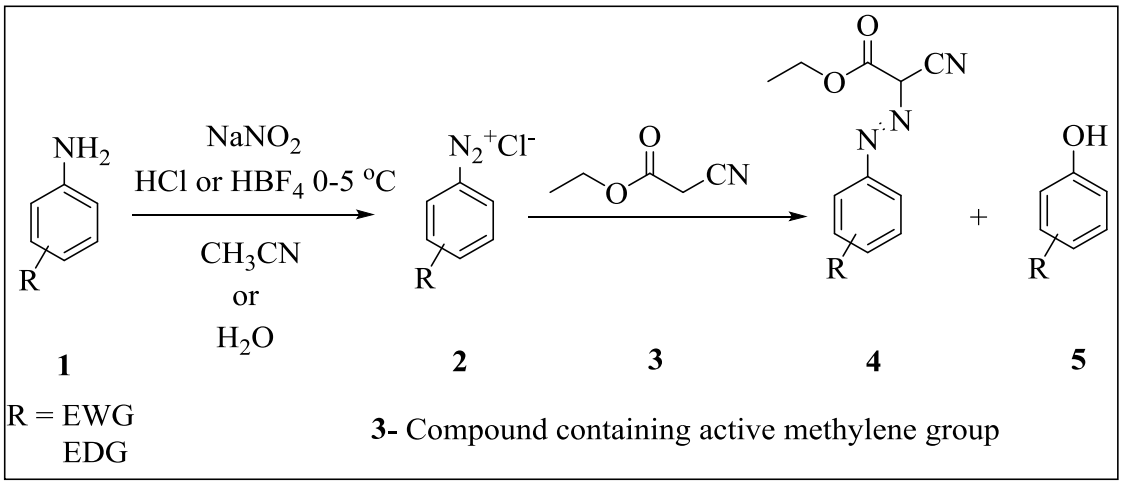
In this work, I will discuss about reaction of nucleophile at β-nitrogen briefly.



Scheme 15: Different reaction of arenediazonium ion

1.5.1 Reaction of Diazonium Salts with Nucleophile at β-nitrogen

Arenediazonium salts react with strong nucleophiles to give azo adducts[18]. Diazonium ions are relatively weak electrophiles, hence, for azo coupling to happen, the coupling partner should be electron rich with high electron density at one or more carbon atoms. Therefore, diazonium ions react at aliphatic carbon atoms, which are activated by electron-withdrawing groups. Azo coupling happens with component, which contains activated methyl group. In the reaction between any nucleophile with arenediazonium ion, kinetically controlled *cis* azo compound and thermodynamically stable *trans* isomers are possible[8]. If the nucleophile is a more reactive, the transition state-of the coupling reactions will come earlier; whereas for a less reactive nucleophile (such as aromatic amines or phenols), it will be a late trasition state. Thus, the stability of the products will be less important in the former case, which yields the kinetically-controlled products, *cis* isomers[18].



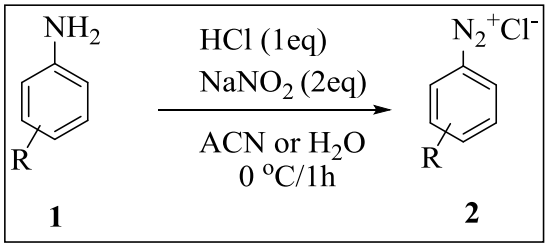
Scheme 16: Reaction of diazonium salts with nucleophile at β-nitrogen

CHAPTER 2

Results and Discussion

Our first target was to make diazonium salt from aniline. Arenediazonium salts are highly polar and mainly soluble in water or highly polar solvent. So, we performed the reaction using a condition based on aqueous medium. Under aqueous conditions, phenol will be a side product along with azo compound, in case the temperature is raised above 5 ^{o}C. This is due to the fact that water will act as a better nucleophile that substitutes the diazonium ion. So, the temperature and amount of water present in the reaction medium are critical in generating diazonium salt. The condition needs to be optimized for generating stable diazonium salt, and for reacting with the active methylene compounds to obtain our targets.

2.1 Preparation of arenediazonium salt



Scheme 17: Preparation of arenediazonium salt

The following conditions were used to get maximum amount of diazonium salt:

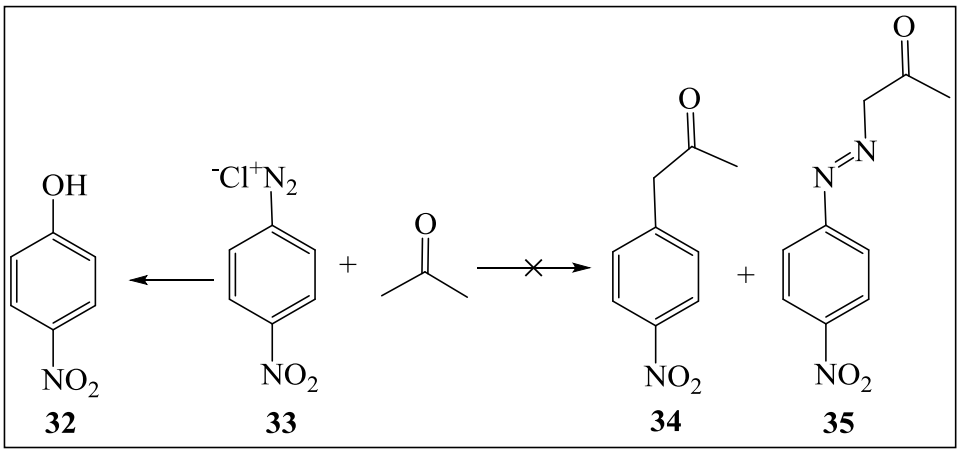
1) Aniline hydrochloride salt was prepared by adding HCl in aniline then followed by dropwise adding of sodium nitrite in 1 ml water at 0 ^{o}C.
2) Sodium nitrite was added in aniline followed by slowly dropwise addition of HCl at 0 ^{o}C.
3) HCl was added to aniline followed by pinch wise addition of sodium nitrite at 0 ^{o}C.

In all cases, arenediazonium salt was obtained. But in case **1** rate of diazotization was faster than others because of the solubility of sodium nitrite in water. Method **1** is most efficient to get maximum amount of diazonium salt and the phenol formation is highly reduced in method **1**.

2.2 Target 1: *C*-arylation

The next target in our project was to perform arylation of certain α-hydrogen containing compounds such as acetone, acetonitrile and ethyl acetate etc. Besides the C-arylated products, the azo coupled product was also expected. However, in all the cases, the reaction of arenediazinium salt with those compounds lead to phenols instead of our expected *C*-aylated and azo-coupled products. For optimization of reaction conditions, following reactions were performed.

2.2.1 Arylation reaction of arenediazonium salt with acetone

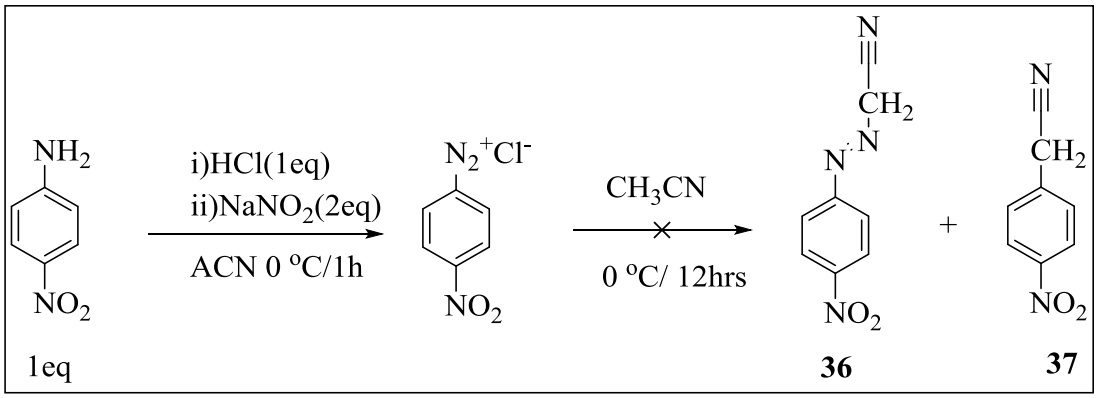


Scheme 18: Arylation reaction of arenediazonium salt with acetone

In the above reaction of *p*-nitrobenzenediazonium chloride with acetone, the desired products were not formed. *p*-nitrophenol was formed instead as a major product because acetone is a week nucleophile and also due to the presence of water in the reaction medium.

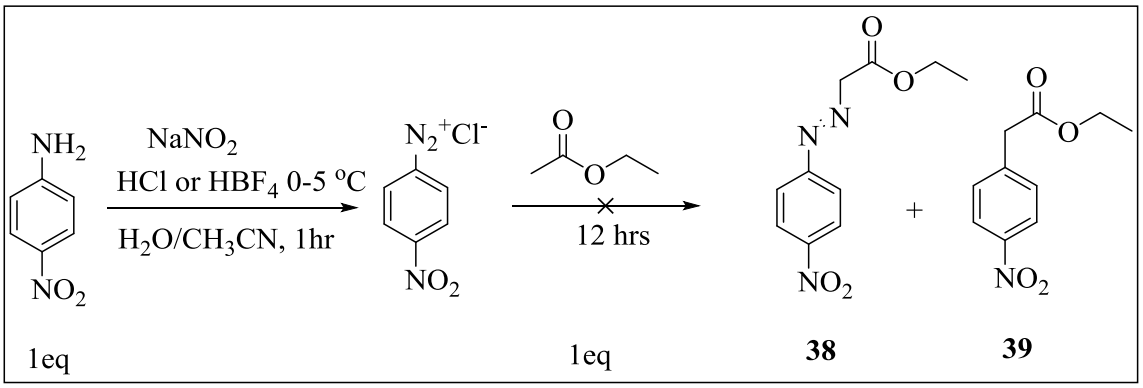
2.2.2 Arylation reaction of arenediazonium salt with acetonitrile

From a wide range of conditions, we found out that acetonitrile did not react with a diazonium salt. So we can utilize acetonitrile as a solvent in the diazotization reactions.



Scheme 19: Arylation reaction of arenediazonium salt with acetonitrile

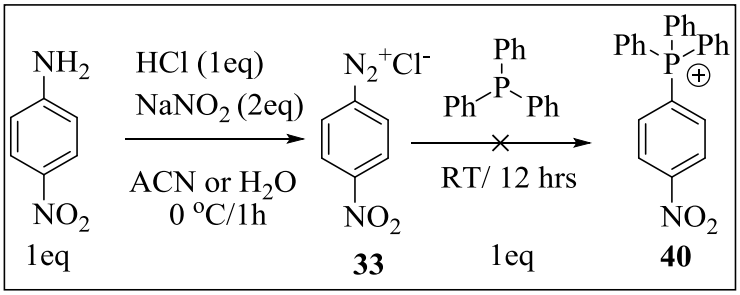
2.2.3 Arylation reaction of arenediazonium salt with ethyl acetate.



Scheme 20: Arylation reaction of arenediazonium salt with ethyl acetate.

Ethyl acetate also did not react with arenediazonium salt. Instead of the expected formation of azo compound or *C*-arylated products, *p*-nitrophenol was formed in all the conditions that we tried.

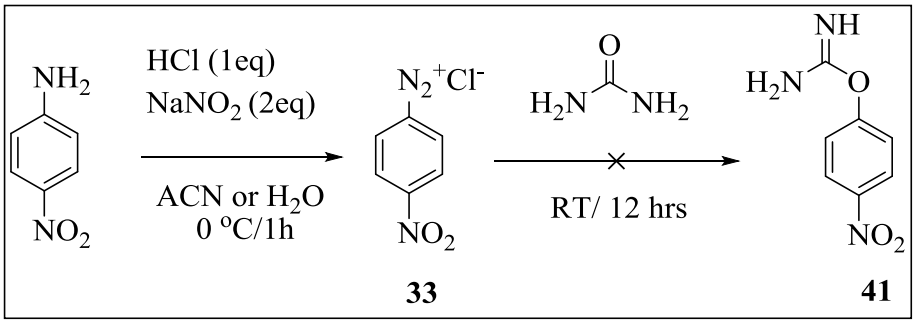
2.3 Reaction of 4-nitroaniline with triphenylphosphine



Scheme 21: Reaction of 4-nitroaniline with triphenylphosphine

In a simillar attempts, we tried to react diazonium salts with triphenylphosphine. However, instead of the expected tetra arylphosphonium salt, triphenylphosphine oxide was formed, which can be due to aerial oxidation under the reaction conditions.

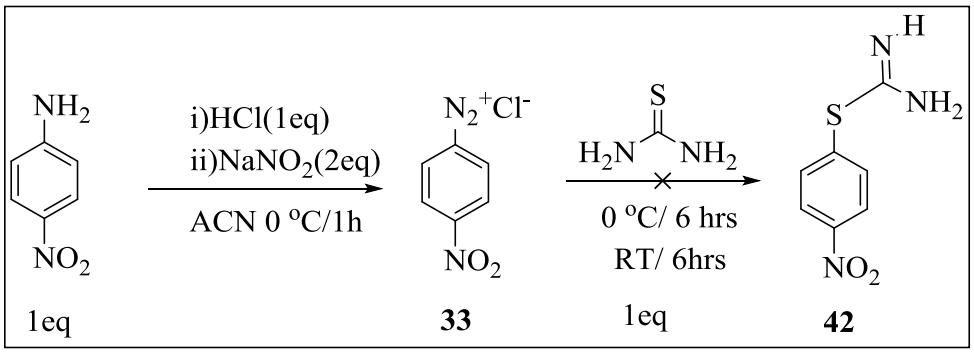
2.4 Reaction of 4-nitroaniline with urea



Scheme 22: Reaction of 4-nitroaniline with urea

We have also tried the reactions of diazonium salts with thiourea to obtain *O*-arylated product. However, we could not obtain the expected product. Instead we could get only the as phenol.

2.5 Reaction of 4-nitroaniline with thiourea

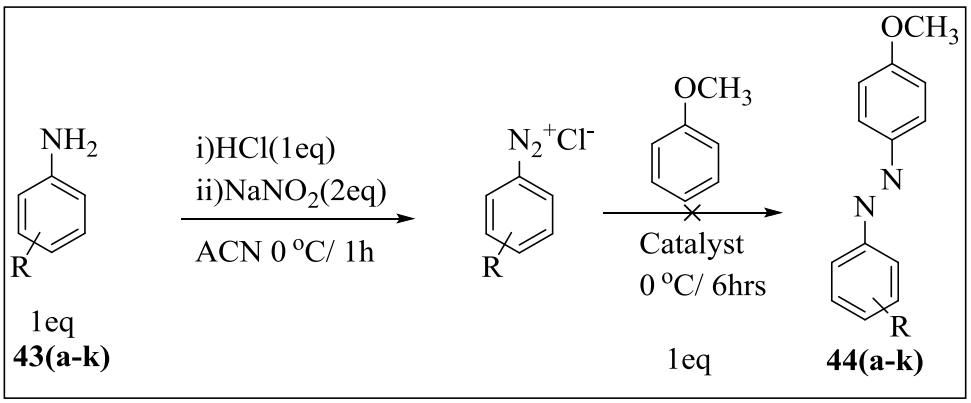


Scheme 23: Preparation of phenyl carbamimidothioate

We have also tried the reactions of diazonium salts with thiourea to obtain *S*-arylated product. However, we could not obtain the expected product. Instead we could get only the as phenol.

2.6 Azo coupling

2.6.1 Azo coupling of different different diazonium salts with anisole



Scheme 24: Azo coupling of different different diazonium salts with anisole

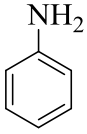
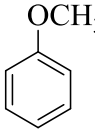
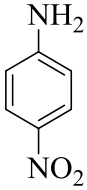
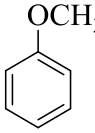
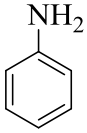
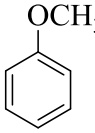
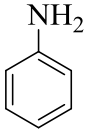
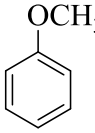
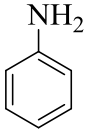
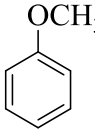
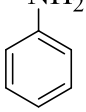
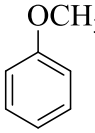
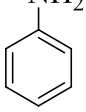
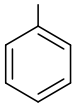
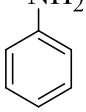
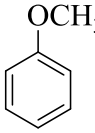
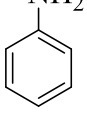
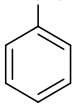
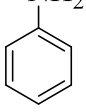
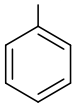
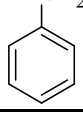
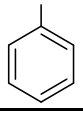
The reaction of various arenediazonium salts with anisole was carried out under different conditions. Reactions of **44a & 44b** were carried out with different catalysts as indicated in the Table 1. In the reaction, a polar spot was observed but anisole was present in reaction mixture so the reaction was continued at room tempeture for longer duration. However, anisole was not consumed at all. Upon TLC monitoring, three new spots were observed; among them one spot was iodine active, whereas the other two spots were UV active. One of the products was found to be phenol. One yellow spot was there on TLC that could be our azo products but due to fewer amounts that spot couldn't isolate.

Then we wanted to see the effect of a catalyst on those reactions, so the reactions were carried out with different catalyst listed in the table in entries **44c-44g**, but in every case diazonium salt and anisole were not consumed completely at all.

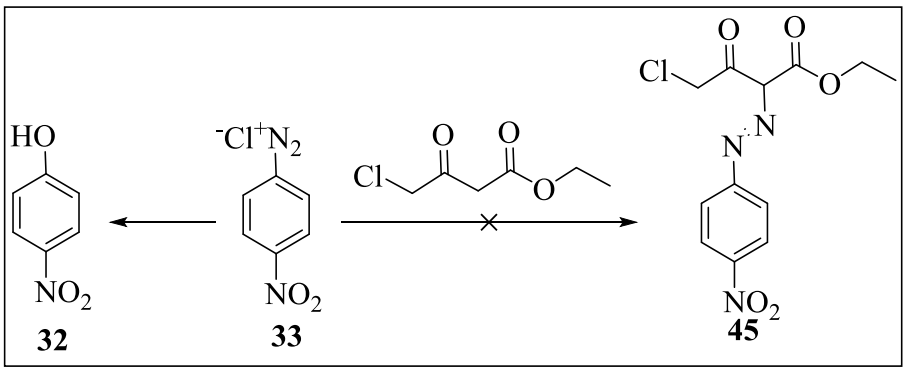
Then we checked the effect of increasing the amount of catalysts in reaction, however the conversion was not improved at all. (Listed in entries **44h & 44i**).

Apart from that we also checked the effect of amount of solvent in the reaction, but again there is no influence in the consumption of diazonium salt and anisole. (Listed in entry **44j & 44k**).

Table 1: Azo coupling of different diazonium salts with anisole

S.No.	Starting Aniline(A)	Solvent	(B)	Catalyst	TLC spot	Result
44a		CH_3CN		No catalyst	New polar spot	Trace
44b		CH_3CN		No catalyst	New polar spot	Trace
44c		CH_3CN		$FeCl_3$ (10 mol %)	New polar spot	Trace
44d		CH_3CN		$FeCl_3$ (1 eq.)	New polar spot	Trace
44e		CH_3CN		CuI (10 mol %)	New polar spot	Trace
44f		CH_3CN		CuBr (10 mol %)	New polar spot	Trace
44g		CH_3CN		$SnCl_2$ (10 mol %)	New polar spot	Trace
44h		CH_3CN		$FeCl_3$ (1.5 eq.)	New polar spot	Trace
44i		CH_3CN		$FeCl_3$ (2 eq.)	New polar spot	Trace
44j		CH_3CN (2 mL)		$FeCl_3$ (1 eq.)	New polar spot	Trace
44k		CH_3CN (3 mL)		$FeCl_3$ (1 eq.)	New polar spot	Trace

2.6.2 Preparation of ethyl -4-chloro-2-(4-nitrophenyl)diazenyl)-3-oxobutanoate

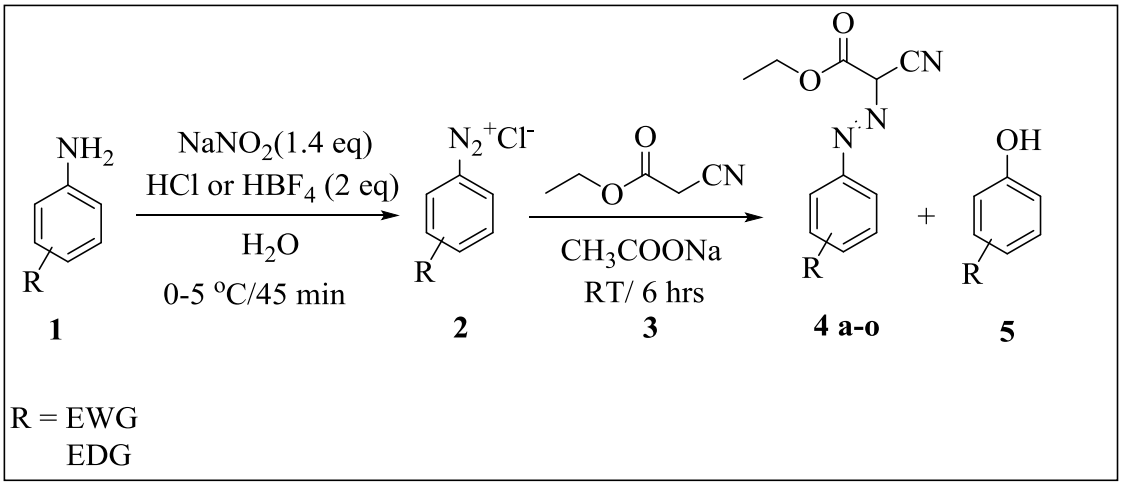


Scheme 25: Preparation of ethyl -4-chloro-2-(4-nitrophenyl)diazenyl)-3-oxobutanoate

In our group, we recently found out that the diazonium salts reacted well with active methylene compounds such as acetylacetone and ethylacetoacetate to form azo compounds. Since none of our reactions of diazonium salts with variety of nucleophiles, aniosole and α-hydrogen containing compounds lead to the expected products, we turned our attention towards active methylene group containing compounds. In this regard, we tried to react diazonium salt with 4-chloroethylacetoacetate. However, under our experimental conditions, 4- nitrophenol was formed instead of the expected azo product.

2.6.3 Azo coupling of ethyl cyanoacetate with different aniline derivatives

In a similar line, diazonium salts of different aniline derivatives were reacted with ethyl cyanoacetate. In almost all the cases, a yellow spot on TLC were detected, which on isolation and characterization, it was found to be our desired azo-coupled product. On the other hand, 2-hydroxy aniline and 3-floroaniline led to a black tarry and sticky product. And in some cases, desired product could not isolated through column chromatography due to the poor yield and difficulty in separating the pure product from close lying polar products. However, we were able to isolate nine different aniline derivative azo-coupled product and the resulting products have been characterized through NMR and HRMS.



Scheme 26: Azo coupling of ethyl cyanoacetate with different aniline derivatives

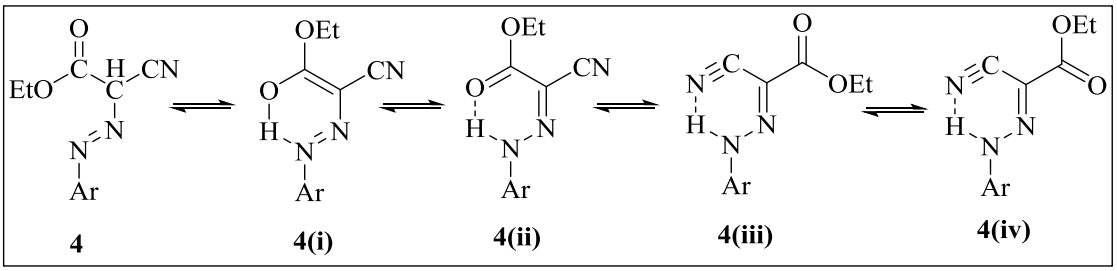
Table 2: Azo-coupling of ethyl cyanoacetate with diazonium salts of anilines derivatives:

S.No.	Starting Aniline	Result	Yield (%)	Tautomer Ratio 4:4(i):4(ii):4(iii):4(iv)
4a	Aniline	Not isolated	-	-
4b	4-nitroaniline	4b	61	0:0:1:0:0
4c	2-nitroaniline	4c	64	0:0:1:0:0
4d	3-nitroaniline	4d	62	0:0:26:74:0
4e	4-chloroaniline	4e	52	0:0:0:1:0
4f	4-methoxyaniline	4f	64	0:0:1:0:0
4g	4-hydroxyaniline	4g	61	0:0:0:70:30
4h	3-hydroxyaniline	4h	62	0:0:0:64:36
4i	3-bromoaniine	Not isolated	-	-
4j	3-floroaniline	Not isolated	-	-
4k	N-(4-aminophenyl)acetamide	4k	68	0:0:71:29:0
4l	2-bromo-3-chloroaniline	Not isolated	-	-
4m	3-aminobenzoic acid	Not isolated	-	-
4n	3-(trifluoromethyl)aniline	Not isolated	-	-
4o	4- aminobenzoic acid	Not isolated	-	-

2.6.4 Tautomerism in azo coupled products of diazonium salts with ethyl cyanoacetate

Interestingly, the product in solution exhibits tautomerism. This can be easily understood from the proton NMR. Some possible tautomer isomer structure is shown in scheme 27. We have investigated the tautomerism in **4d, 4g, 4h** and **4k** using ^{1}H-NMR spectroscopy. For **4d,** the NMR spectra in DMSO-d_6 look very clear and straight forward. The protons corresponding to the aromatic rings were observed between δ 7-8 ppm, whereas ^{1}H-NMR

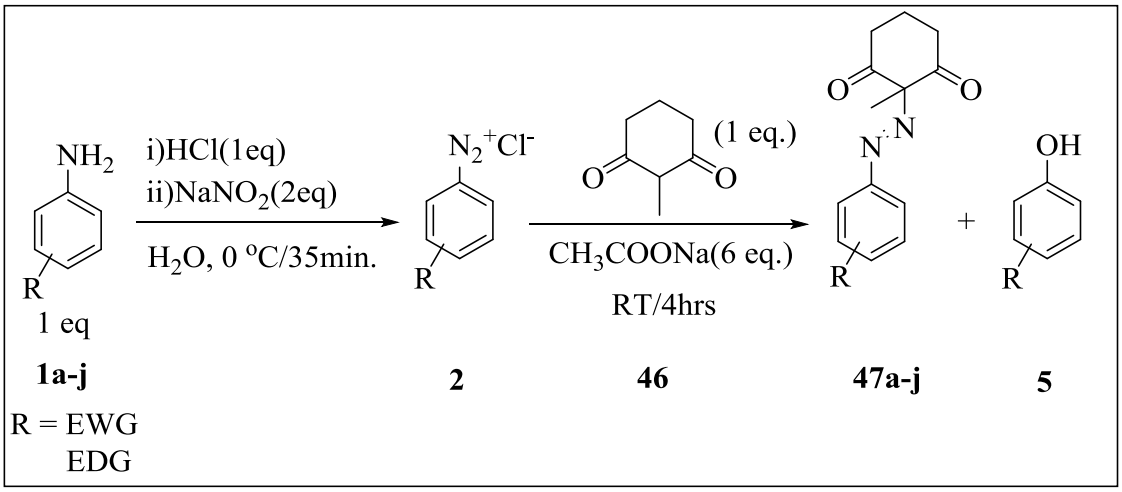
revealed two different singlet for one proton at δ 13.03 ppm and δ 12.53 ppm. The singlet at δ 12.53 ppm is assigned to the NH proton in the hydrazone while singlet at δ 13.03 ppm is assigned to the OH proton in enolazo. The spectrum clearly indicates that the structure is having a fast equilibrium between their tautomers. The similar effect was also observed in the case of **4k.** Where the singlet at δ 10.05 ppm is assigned to the NH proton in the structure **4(iii)** while singlet at δ 12.25 ppm is assigned to the OH proton in hydrazone. Also in **4g** Where the singlet at δ 9.66 ppm is assigned to the NH proton in the structure **4(iv)** while singlet at δ 9.55 ppm is assigned to the NH proton in structure **4(iii)**. And for **4h,** the singlet at δ 9.73 ppm is assigned to the NH proton in the structure **4(iv)** while singlet at δ 9.62 ppm is assigned to the NH proton in structure **4(iii).** In all other cases only one structure is observed with a singlet for NH proton in the hydrazone.



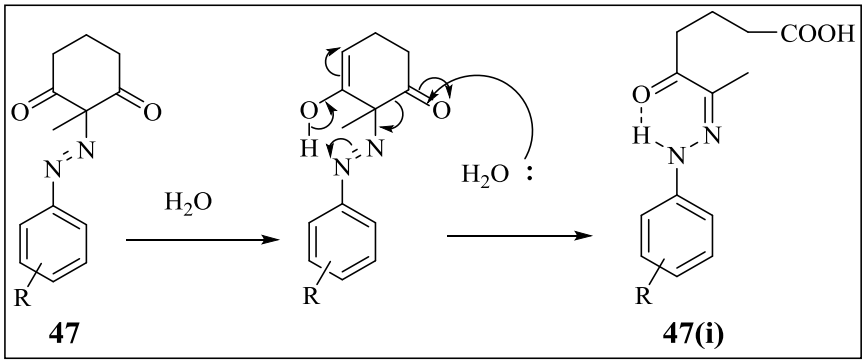
Scheme 27: Tautomerism in azo coupled products of diazonium salts with ethyl cyanoacetate

2.6.5 Azo coupling of methyl cyclohexadione with different aniline derivatives

Azo coupling of diazonium salts with 2-methyl cyclohexadione was also performed under the same conditions as in the case of ethyl cyanoacetate. In almost all the cases, a yellow spot on TLC were detected we could only isolated for 4-choro derivative. However the coupled product hydrolyzed in the presence of water and lead to ring opening, producing a carboxylic acid functionalized product. Because of the interaction of the carboxylic acid with silica mix the purification very difficult by column chromatography. In case of 4-NO_2 derivative, product was only partly soluble in water so we could not characterize that product. However, we were not able to purify the product with other derivatives. The formation of all derivatives was confirmed with the help of NMR of crude reaction mixture.



Scheme 28: Azo coupling of methyl cyclohexadione with different aniline derivatives



Scheme 29: Ring opening mechanism for the formation of product **47**

Table 3: Azo coupling of 2-methyl cyclohexadione with different aniline derivatives

S.No.	Starting Aniline	Solvent	Result	Yield (%)
a.	Aniline	H_2O	Not isolated	-
b.	4-nitroaniline	H_2O	Not isolated	-
c.	2-nitroaniline	H_2O	Not isolated	-
d.	3-(trifluoromethyl)aniline	H_2O	Not isolated	-
e.	4-chloroaniline	H_2O	47e	42
f.	4-methoxyaniline	H_2O	Not isolated	-
g.	4-hydroxyaniline	H_2O	Not isolated	-
h.	3-hydroxyaniline	H_2O	Not isolated	-
i.	4-bromoaniine	H_2O	Not isolated	-
j.	4-floroaniline	H_2O	Not isolated	-

CHAPTER 3

CONCLUSION & PERSPECTIVES

Through this investigation, on exploring the reactivity of diazonium salts with various nucleophiles and enolates, we obtained following conclusions:

- We successfully identified mild condition to synthesis the arenediazonium salt. The phenol formation is highly reduced by using ACN as a solvent.
- Arenediazonium salt was then subjected to rections with various nucleophiles to get arylated products, but was not unsuccessful.
- With anisole azo coupling was tried, however the yields were not improved even after the use of Lewis acids and metal catalysts.
- Extending the same strategy with ethyl cynoacetate, we isolated the corresponding azo products with moderate to good isolated yields. Interestingly, those products showed tautomerism.
- Reactions with 2-methyl cyclohexadione showed ring opening of azo coupled products.

CHAPTER 4

EXPERIMENTAL SECTION

4.1 General Methods:

The solvents and reagents were purchased from commercial suppliers (Sigma-Aldrich, Merck and HiMedia). The reactions monitored by TLC was on run on silica gel plates (Merck) and visualized with UV light and iodine stains. Column chromatography was performed on silica gel (60-120 mesh) purchased from HiMedia. The IR spectra were recorded on a "Perkin Eimer" FT-IR spectrometer. Mass spectra were recorded on a "Water Synapt G2-Si Q ToF Mass Spectrometer" in a positive and negative Electron Spray Ionization mode. The ^{1}H NMR and ^{13}C NMR were recorded on an Avance-III, Bruker Biospin 400 MHz and 100 MHz respectively at room temperature. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or corrected to the residual solvent proton signals. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz).

4.2 Synthesis

4.2.1 General procedure for synthesis of 1-phenylpropan-2-one.

Aniline (100 mg) was taken in a 10 mL round bottom flask. Then conc. HCl (2 eq.) was added slowly and the mixture was cooled using ice (at 0-5 ^{o}C temp.) and stirred. Then 5 mL ACN was added to the reaction mixture. Sodium nitrite (2 eq.) in 1.5 mL H_2O was added dropwise to the reaction mixture for 1hr and allowed to stir on ice for 1 hr. Then acetone (1 eq.) was added and the reaction mixture was allowed to stir on ice for 6 hrs. The reaction was monitored by TLC. Upon completion, the aqueous part was decanted and the solid part was dissolved in ethyl acetate. The organic layer was washed with brine solution and ethyl acetate and then dried with sodium sulphate. The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography to give phenol.

4.2.2 Reaction of 4-nitroaniline with acetonitrile.

Same procedure as 4.2.1 was performed, however, ACN was added instead of acetone. No reaction was observed with acetonitrile.

4.2.3 Reaction of 4-nitroaniline with triphenylphosphine

Same procedure as 4.2.1 was performed. Triphenylphosphine got oxidized in presence of atmospheric oxygen.

4.2.4 Preparation of ethyl (*E*)-2-((4-nitrophenyl)diazenyl)acetate

Same procedure as 4.2.1 was performed ethyl acetate didn't react with aniline.

4.2.5 Preparation of ethyl -4-chloro-2-(4-nitrophenyl)diazenyl)-3-oxobutanoate

Same procedure as 4.2.1 was performed ethyl 4-chloro-3-oxobutanoate didn't react with aniline.

4.2.6 Preparation of phenyl carbamimidothioate

Same procedure as 4.2.1 was performed thiourea didn't react with aniline.

4.2.7 Azo coupling of anisole with different aniline derivatives

Aniline (100 mg) was taken in a 10 mL round bottom flask. Then conc. HCl (2 eq.) was added slowly and the mixture was cooled using ice (at 0-5 ^{o}C temp.) and stirred. Then 5 mL ACN was added to the reaction mixture. Sodium nitrite (2 eq.) in 1.5mL H_2O was added dropwise to the reaction mixture for 1hr and allowed to stir on ice for 1 hr. Then anisole (1 eq.) was added and the reaction mixture was allowed to stir on ice for 6 hrs then the reaction was monitored by TLC. Then reaction mixture was allowed to stir on RT for 6 hrs and reaction was monitored by TLC. In reaction **44c** $FeCl_3$ (10 mole %), **44d** $FeCl_3$ (1 eq.), **7e** CuI (10 mole %), **44f** CuBr (10 mole %), **44g** $SnCl_2$ (10 mole %), **44h** $FeCl_3$ (1.5 eq.), **44i** $FeCl_3$ (2 eq.), **44j & 44k** $FeCl_3$ (1 eq.), respectively added as catalyst. Upon completion, the aqueous part was decanted and the solid part was dissolved in ethyl

acetate. The organic layer was washed with brine solution and ethyl acetate and then dried with sodium sulphate. The solvent was then evaporated under reduced pressure. The mixture was checked by TLC but Anisole didn't react with arenediazonium salt.

4.2.8 Azo coupling of ethyl cyanoacetate with different aniline derivatives.

Aniline (100 mg) was taken in a 10 mL round bottom flask. Then conc. HCl (2 eq.) was added slowly and the mixture was cooled using ice (at 0-5 ^{o}C temp.) and stirred. Then 5 mL water was added to the reaction mixture. Sodium nitrite (1.4 eq.) in 1.5 mL H_2O was added drop wise to the reaction mixture for 20 min and allowed to stir on ice for 30 min. Then ethyl cynoacetate (1 eq.) with sodium acetate (6 eq.) in cold water was added and the reaction mixture was allowed to stir on ice for 6 hrs. The reaction was monitored by TLC. Upon completion, the aqueous part was decanted and the solid part was dissolved in ethyl acetate. The organic layer was washed with brine solution and ethyl acetate and then dried with sodium sulphate. The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography yellow azo products. Same procedure was followed with different aniline derivatives to get desired azo-coupled product.

Ethyl 2-cyano-2-(2-(4-methoxyphenyl)hydrazono)acetate (4f)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.22 (s, 1H), 7.29-7.31 (d, J = 8.84Hz, 2H), 6.93-6.95 (d, J = 8.88Hz, 2H), 4.34-4.39 (q, 2H), 3.84 (s, 3H), 1.40-1.43 (t, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ (ppm) 162.92, 158.00, 134.47, 117.17, 114.87, 103.03, 62.11, 55.61, 14.13; FTIR (KBr) cm^{-1} : 3270 (NH), 2932 (C=C-H), 1744 (C=O), 2231 (CN); m/z $(M+H)^{+}$: 248.1033

Ethyl 2-cyano-2-(2-(4-nitrophenyl)hydrazono)acetate (4b)

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.58 (s, 1H), 7.61-7.64 (d, J = 9.20Hz, 2H), 8.28-8.30 (d, J = 9.24, 2H), 4.29-4.35 (q, 2H), 1.29-1.33 (t, 3H); FTIR (KBr) cm^{-1}: 3352 (NH), 2969 (C=C-H), 1719 (C=O), 2224 (CN), 1555, 1372 (NO); m/z $(M+H)^{+}$: 263.0779

Ethyl 2-(2-(4-chlorophenyl)hydrazono)-2-cyanoacetate (4e)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.59 (s, 1H), 7.37-7.39 (d, J = 9Hz, 2H), 7.32-7.34 (d, J = 8.96Hz, 2H), 4.39-4.45 (q, 2H), 1.40-1.43 (t, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 14.25, 62.50, 106.23, 110.31, 117.08, 129.80, 130.93, 139.08, 160.25; FTIR (KBr) cm^{-1}: 3358 (NH), 2993 (C=C-H), 1712 (C=O), 2359 (CN), 772 (Ar-Cl); m/z $(M+H)^{+}$: 252.0546: M.P.- 84-88 ^{o}C.

Ethyl 2-cyano-2-(2-(3-nitrophenyl)hydrazono)acetate (4d)

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.53 (s, 1H), 8.28 (s, 1H), 7.97-7.99 (d, 1H), 7.85-7.87 (dd, J = 8.12Hz, 1H), 7.67-7.71 (d, 1H), 4.29-4.37 (q, 2H), 1.29-1.35 (t, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 160.84, 160.16, 148.93, 143.58, 131.37, 122.81, 120.03, 119.29, 106.50, 62.35, 14.55; FTIR (KBr) cm^{-1}: 3370 (NH), 2969 (C=C-H), 1738 (C=O), 2227 (CN), 1570, 1398 (N=O); m/z $(M+H)^{+}$: 263.0781.

Ethyl (*Z*)-2-(2-(4-acetamidophenyl)hydrazono)-2-cyanoacetate (4k)

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.25 (s, 1H), 10.02 (s, 1H), 7.60-7.62 (d, J = 8.96Hz, 2H), 7.40-7.42(d, J = 8.92, 2H), 4.25-4.32(q, 2H), 2.04 (s, 3H), 1.27-1.33(t, 3H); FTIR (KBr) cm^{-1}: 3358 (NH), 2993 (C=C-H), 1712 (C=O), 2227 (CN); m/z $(M+H)^{+}$: 275.2877

Ethyl 2-cyano-2-(2-(4-hydroxyphenyl)hydrazono)acetate (4g)

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.02 (s, 1H), 12.17 (s, 1H), 9.66 (s, 1H), 9.55 (s, 1H), 7.31-7.33 (d, J = 8.92Hz, 2H), 6.78-6.81 (d, J = 8.88Hz, 2H), 4.24 (q, 2H), 1.32 (t, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 161.81, 156.33, 134.62, 118.27, 116.34, 112.41, 102.33, 62.07, 14.67; FTIR (KBr) cm^{-1}: 3371 (NH), 2959 (C=C-H), 1730 (C=O), 2234 (CN), 3278 (OH); m/z $(M+H)^{+}$: 234.0883.

Ethyl 2-cyano-2-(2-(3-hydroxyphenyl)hydrazono)acetate (4h)

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.18 (s, 1H), 9.62 (s, 1H), 7.35 (s, 1H), 7.30-7.33 (d, 1H), 6.79-6.81 (m, 2H), 4.23-4,27 (q, 2H), 1.29-1.31(t, 3H); FTIR (KBr) cm^{-1}: 3380 (NH), 2969 (C=C-H), 1738 (C=O), 2260 (CN), 3310 (OH) ; m/z $(M+H)^{+}$: 234.0876.

Ethyl 2-cyano-2-(2-(2-nitrophenyl)hydrazono)acetate (4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 12.27 (s, 1H), 8.09-8.30 (d, J = 3.28Hz, 1H), 7.73-7.77(t, 1H), 7.29-7.31 (t, 1H), 7.27-7.28 (d, 1H), 4.43-4.48 (q, 2H), 1.42-1.46 (t, 3H); FTIR (KBr) cm^{-1}: 3235 (NH), 2968 (C=C-H), 1738 (C=O), 2342 (CN), 1586,1372 (N=O); m/z $(M+H)^+$: 263.0781.

4.2.9 Azo coupling of 2-methylcyclohexane-1,3-dione with different aniline derivatives

Same procedure as 4.2.8 was followed.

(*Z*)-6-(2-(4-chlorophenyl)hydrazono)-5-oxoheptanoic acid (47e)

^{1}H NMR (400 MHz, CDCl3): δ (ppm) 7.44 (s, 1H), 7.30-7.32 (d, J = 8.7, 2H), 7-15-7.17 (d, J = 8.8 2H), 3.03-3.07 (t, 2H), 2.46-2.48 (t, 2H), 2.02-2.05 (m, 2H), 2.02 (s, 3H); FTIR (KBr) cm^{-1}: 3435 (OH), 3276 (NH), 1711 (Carboxylic Acid CO), 1656 (Ketone CO)

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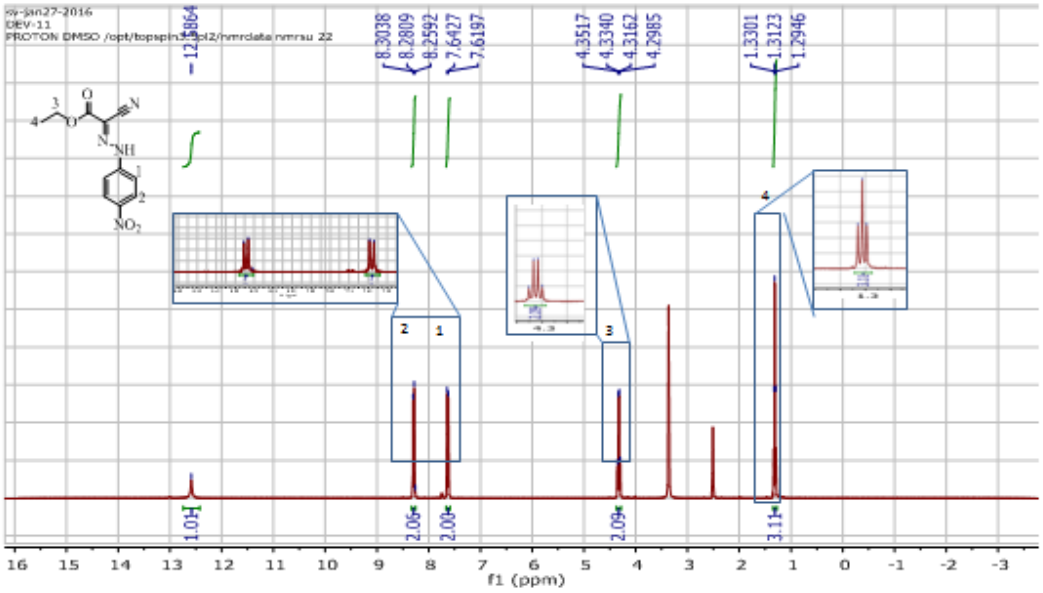
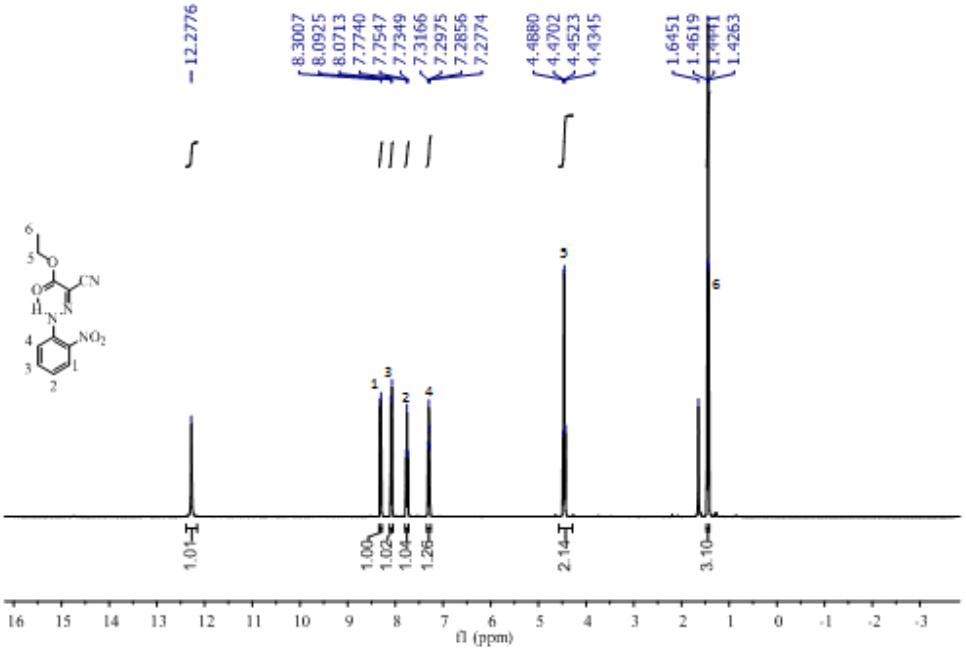
APPENDIX

NMR DATA

^{1}H-NMR Ethyl 2-cyano-2-(2-(4-nitrophenyl)hydrazono)acetate (4b)



^{1}H-NMR Ethyl 2-cyano-2-(2-(2-nitrophenyl)hydrazono)acetate (4c)



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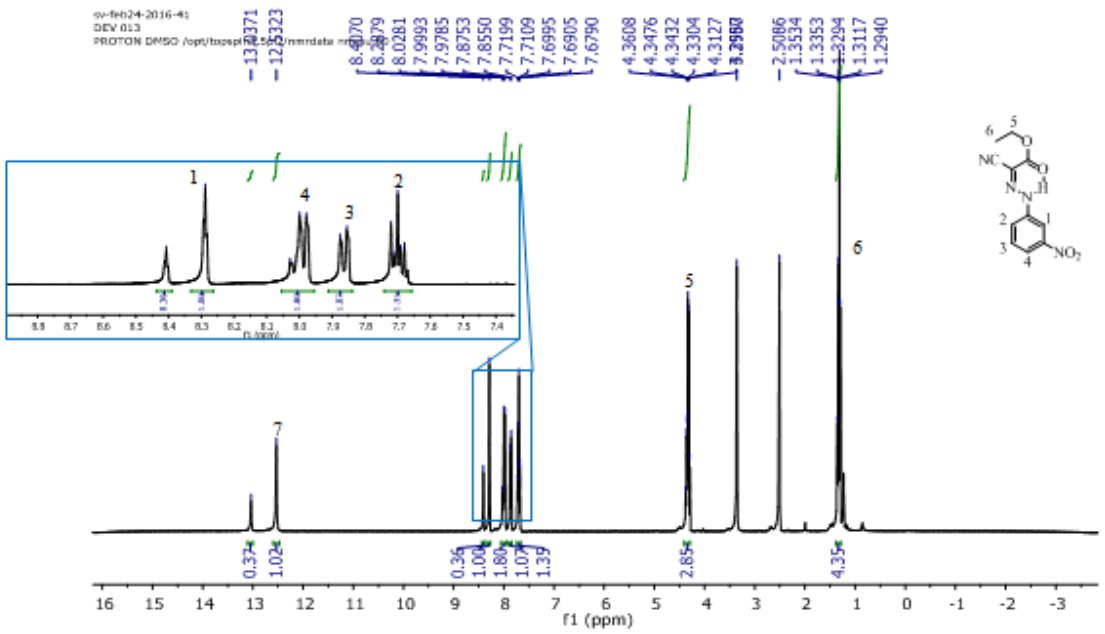

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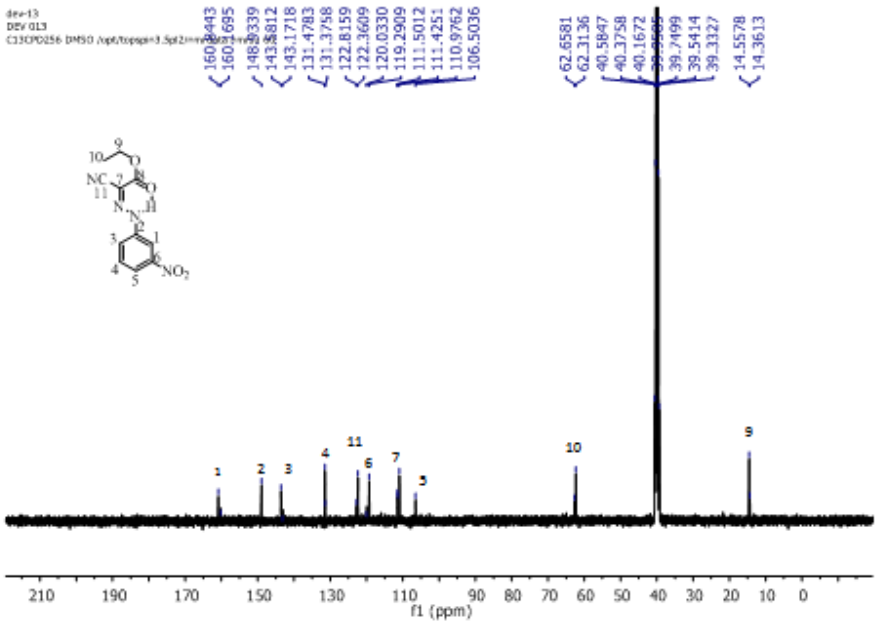

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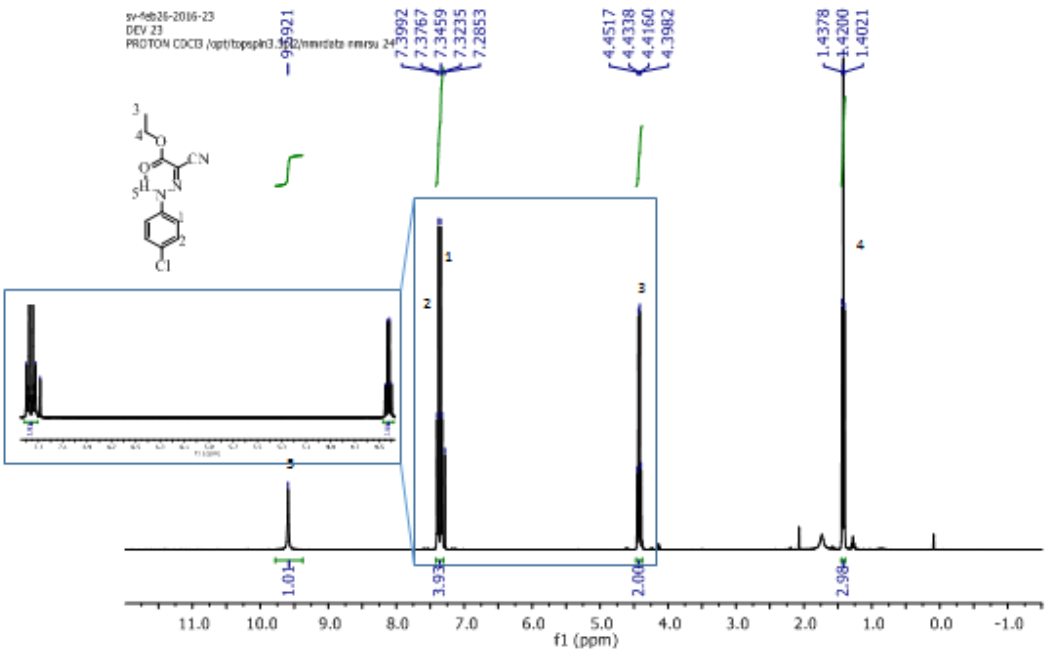

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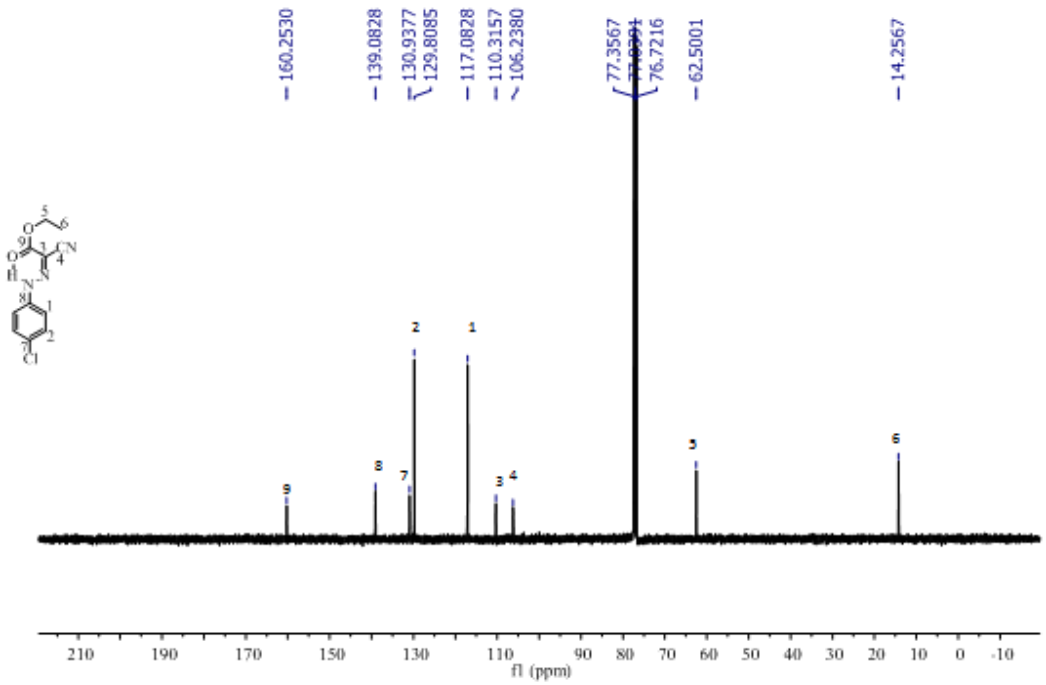

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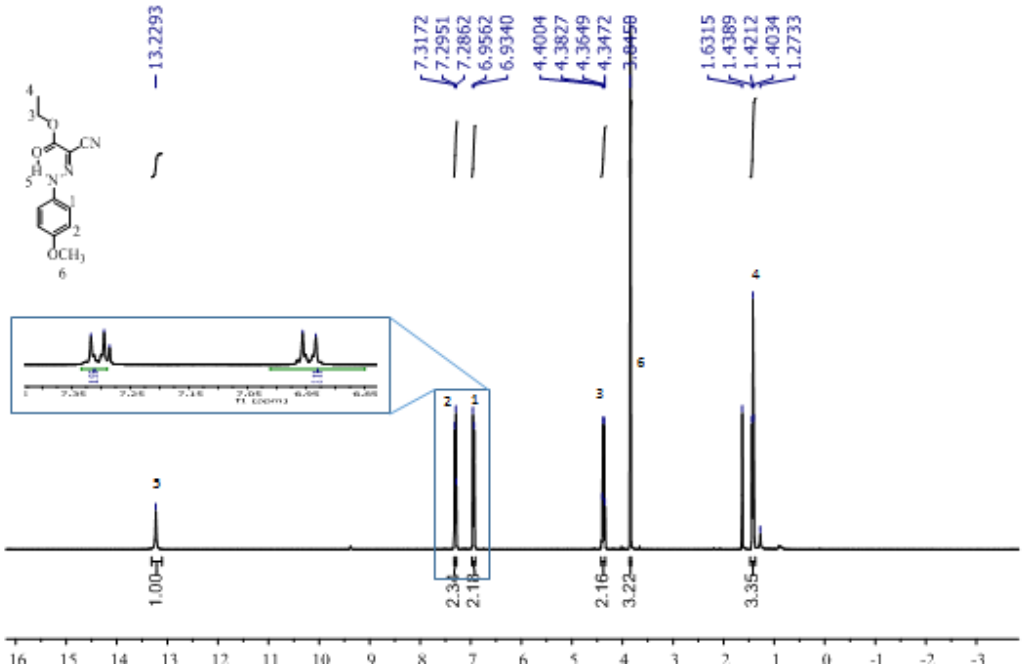

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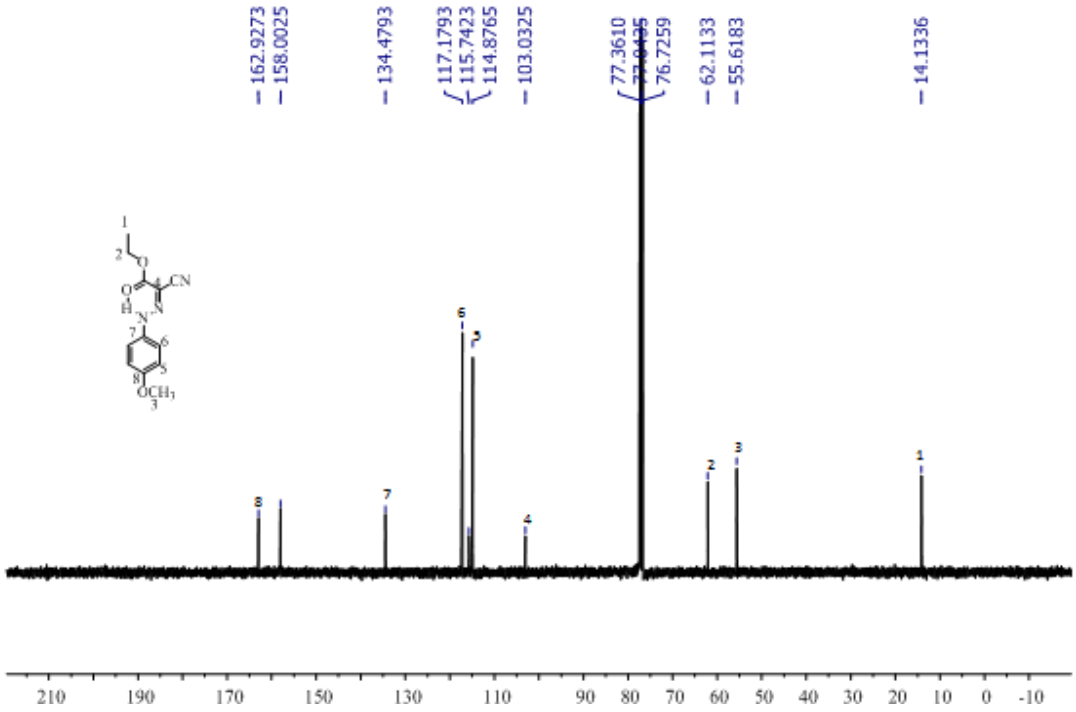

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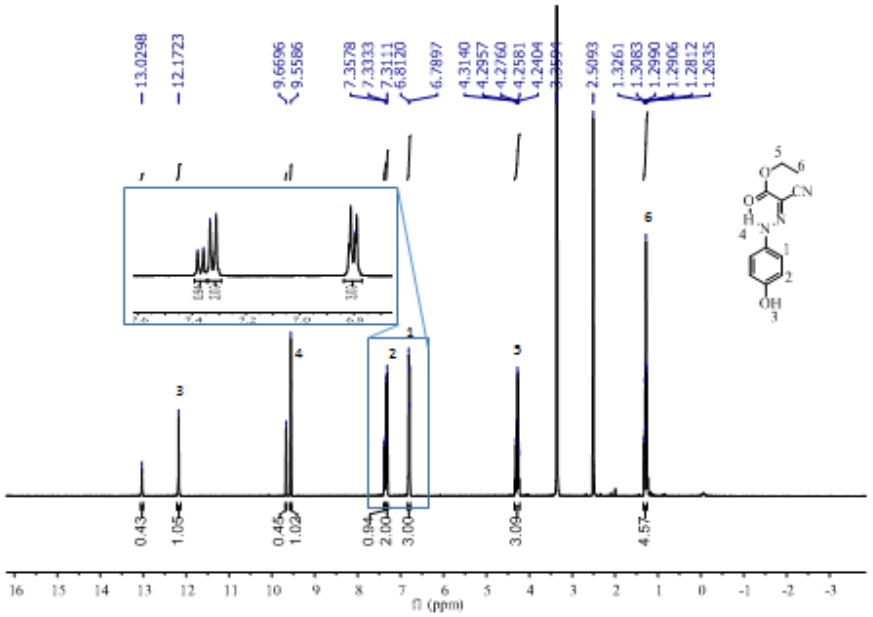

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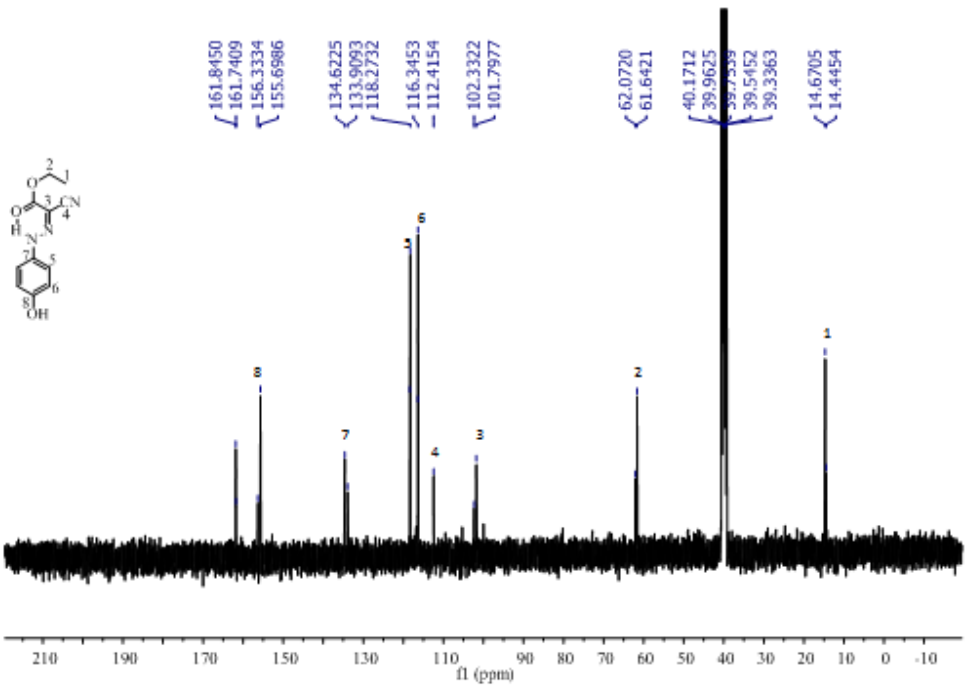
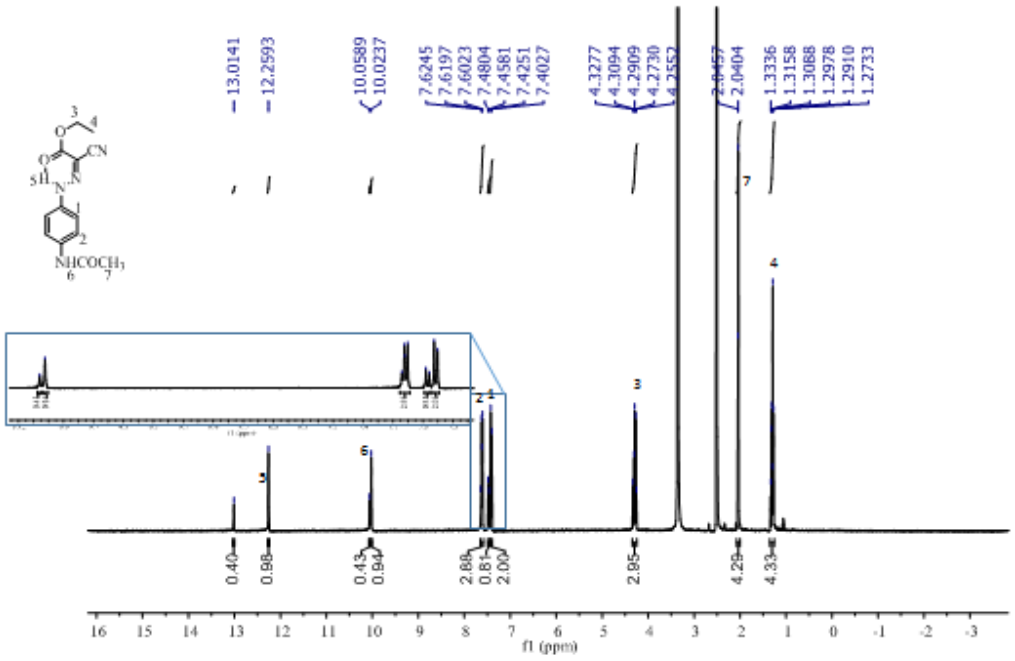


^{1}H-NMR of Ethyl (*Z*)-2-(2-(4-acetamidophenyl)hydrazono)-2-cyanoacetate (4k)



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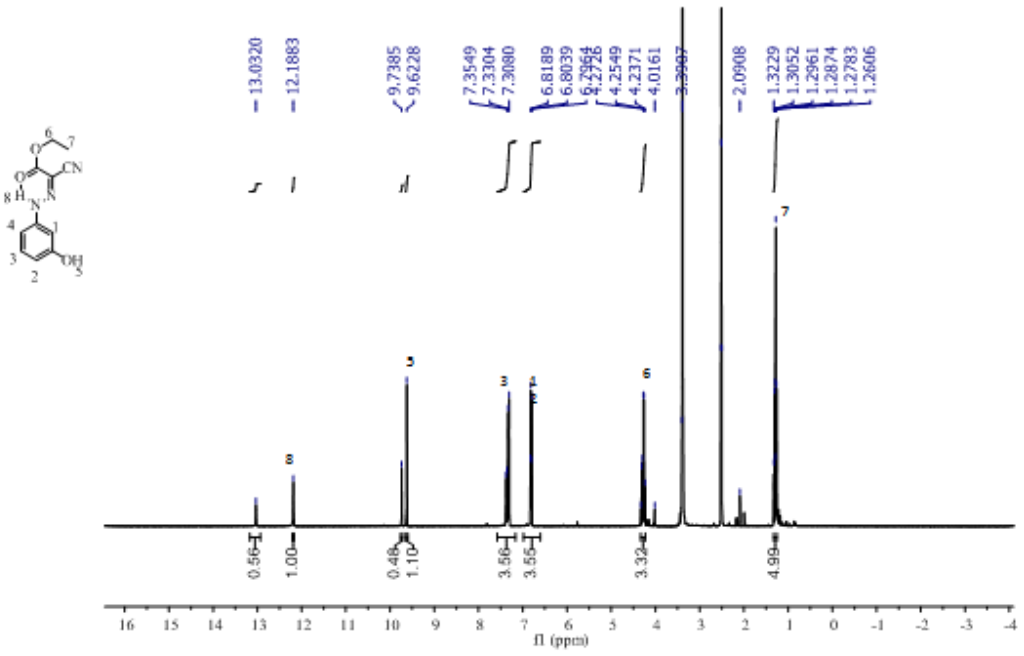

[1]H-NMR of (*Z*)-6-(2-(4-chlorophenyl)hydrazono)-5-oxoheptanoic acid (47e)