Benghazi University
Faculty of science
Department of chemistry

SYNTHESIS OF PYRAZOLE AZO DYES

A thesis submitted as partial fulfillment for the requirements of the degree of Master of Science in chemistry

By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَىٰ وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ

صَدَقَ اللَّهُ الْعَظِيمْ

الآية (١٩) من سورة النمل

Acknowledgement

Praise is to god, lord of the universe, by his will the accomplished of this work, also I am particularly grateful to prof.Dr. Abdalla H.Gheath, That provided me with guidance, and the perpetual support, so my thanks and my appreciation to staff members of chemistry department, and thanks to my family and all my friends.

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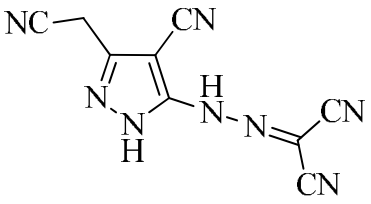
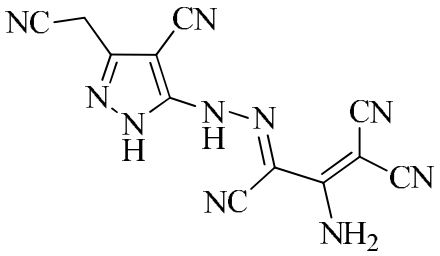
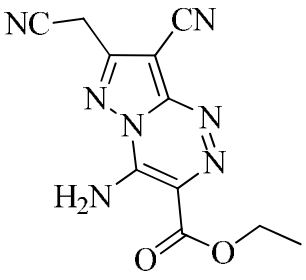
ABSTRACT

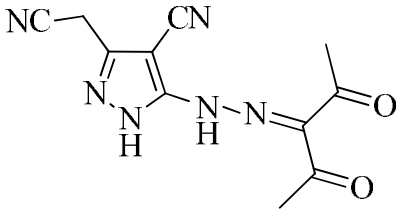
Diazotization of 5-amino-3-(cyanomethyl)-1H- pyrazole-4-carbonitrile in presence of sodium nitrite and hydrochloric acid at 0^{o}C allowed to react with different compounds containing methylene group in presence of sodium acetate and ethanol, which act as a nucleophilic center and attack the diazonium salt of pyrazole to yield corresponding azo dyes of pyrazol, so the value of the pH is very effective in synthesis of azo dyes, where coupling reaction of pyrazole with malononitrile, ethyl cyano acetate, acetylacetone and MND in sodium acetate as buffere

afforded the following:

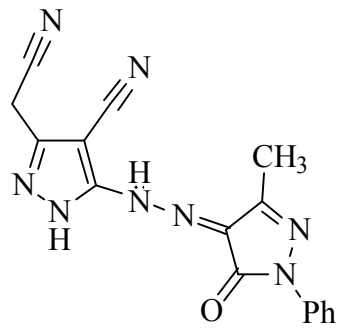


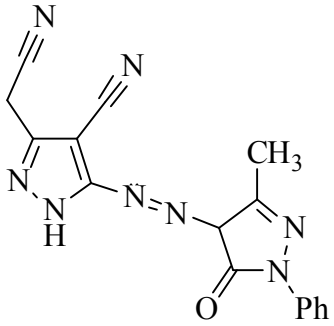


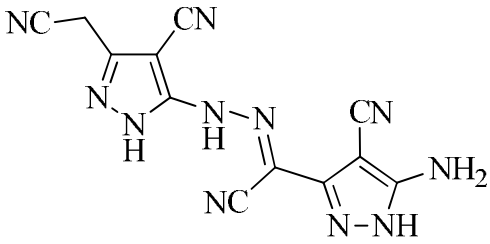


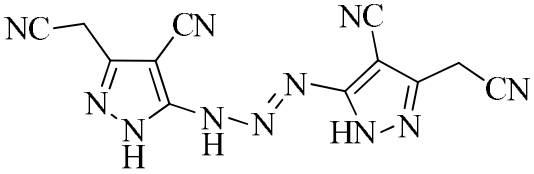


whereas there are several possibilities for the precipitation of products, depending on the value of the pH through coupling reaction between diazonium salt of pyrazole with 3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one, and coupling reaction of pyrazole with its counterpart as follows.









ABBREVATION:

EtOH	Ethanol
HCl	Hydrochloric acid
NaOAc	Sodium acetate
MND	Malononitril dimer
Ethyl acetoacetate	EAA
DEPT	Distortionless Enhancement by Polarization Transfer
TLC	Thin Layer Chromatography
DMF	Di Methyl Formamide

Notes

- Compounds synthesized in this M.Sc. thesis are written in Roman numbers.
- Compounds which are known in literature and synthesized or used in parts of this work are written in Arabic numbers.

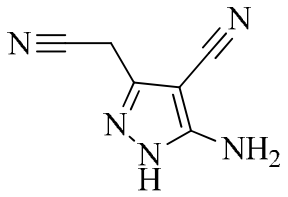
CONTENTS

Chapter one

INTRODUCTION

1.1. INTRODUCTION:

In recent years pyrazole derivatives have received significant attention owing to their diverse range of biological properties particularly being antifungal, antitubercular, antibacterial, antiviral, anticancer and antioxidant[1,2].The chemistry of amino pyrazole compounds present in many of the applications, most important biologically active compounds used in agriculture and medicine, as well intermediates in the synthesis of new classes of poly condensed heterocyclic compounds[3].

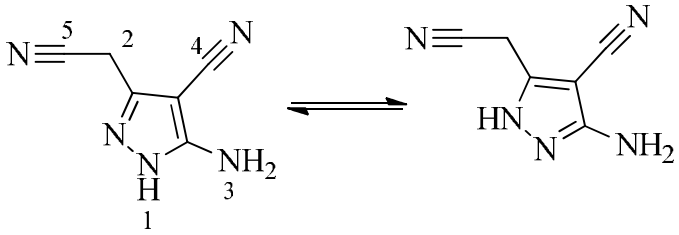


(1)

A number of reactions of pyrazole were described illustrating its versatility as an intermediate for the synthesis of condensed pyrazole heterocycles and used to form a large number of heterocyclic compounds of a character indicating the presence of bicyclic and tricyclic systems via many reactions including the active groups in the compound.

5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile is a π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms in

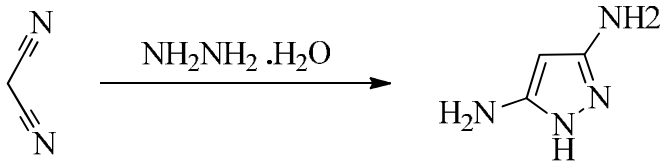
a five membered 1,2-diazole ring, there are three sites for electrophilic attack the NH group [1] of pyrazole ring (1a) which are in tautomeric equilibrium with (1b), the active methylene group [2] and the amino group [3], whereas two such sites are available for nucleophilic attack the carbon atom of the conjugated nitrile group [4] and the carbon atom of the nonconjugated nitrile group [5].



(1a) (1b)

1.2.Synthesis of 5-amino-3-(cyanomethyl)-1H pyrazole-4-carbonitrile:

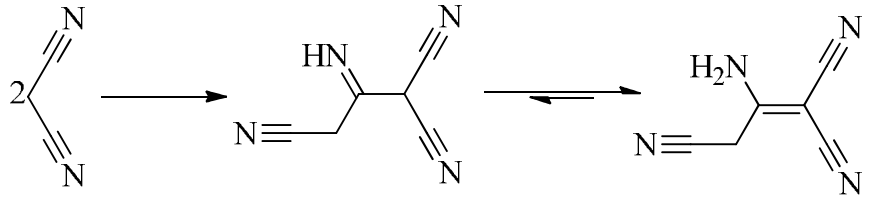
The first attempt was in1894 Rothenburg suggest that malononitrile reacted with hydrazine hydrate to yield 3,5-diaminopyrazole (2). Von Rothenburg failed to notice that the reaction was accompanied by the evolution of ammonia[4,5].



(2)

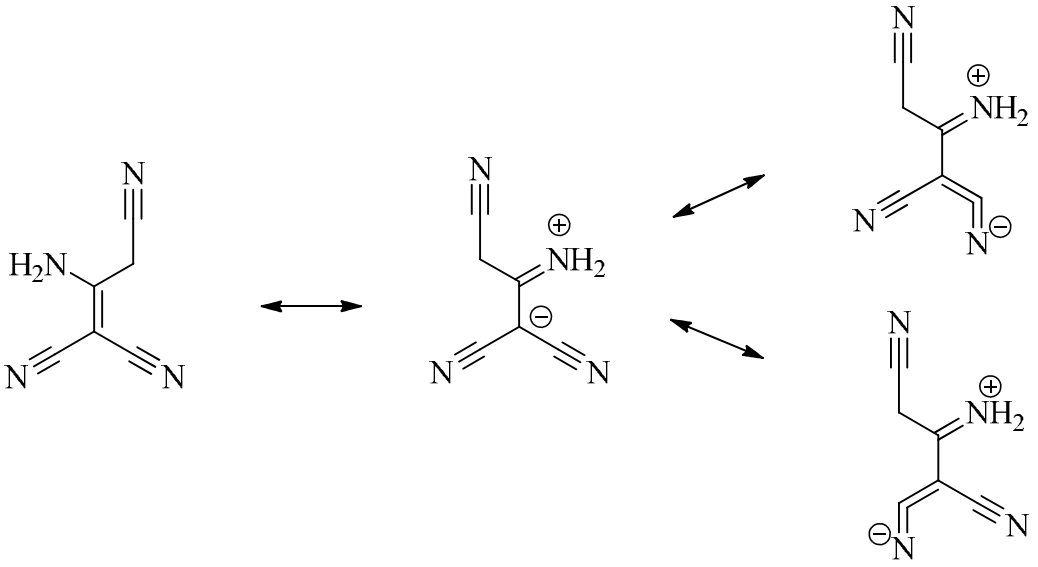
After years co-workers have demonstrated that the product was already (1) formed via dimerisation of malononitrile to yield malononitrile dimer (1,1,3-tricyano-2-amino-1-propene) [6,7,8,9](3).

The mechanisum of reaction proposed that the removal of a proton from the active methylene group in malononitrile followed by nucleophilic addition of this anion to the unsaturated carbon of a second malononitrile molecule yielding a ketamine (3a) where would prefer tautomerize to the more stable conjugated enamine[10] (3).

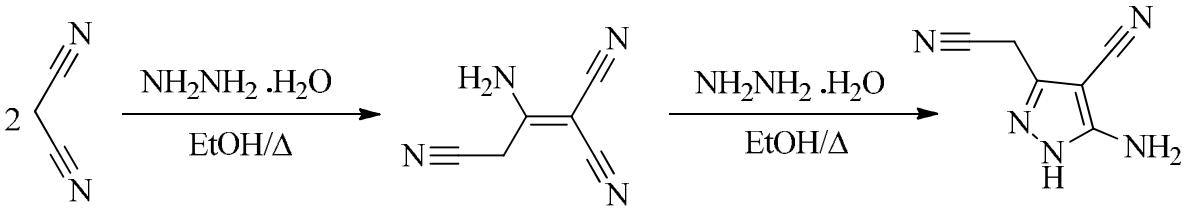


(3a) (3)

Compound (3) appears as one of several zwitterionic forms stabilized by resonance:



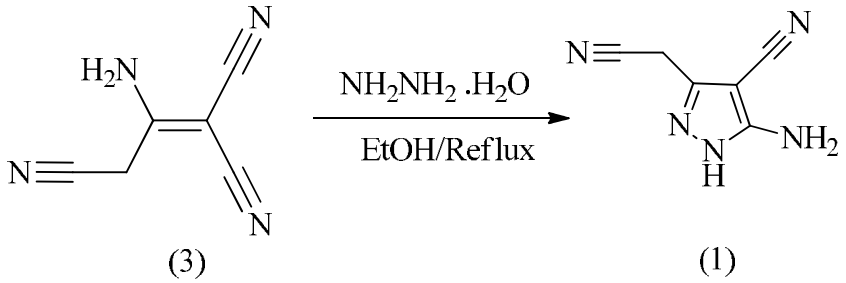
The reaction of malononitrile or malononitrile dimer with hydrazine hydrate gave 5-amino-3-(cyanomethyl)-4-cyano-1H-pyrazole[7,11,12] (1) as following:



(3) (1)

The product was formed from two moles of malononitrile and one mole of hydrazine hydrate with loss of one mole of ammonia yielded 40 %. The best method reaction of malononitrile dimer with hydrazine hydrate yielded

71.5 %.



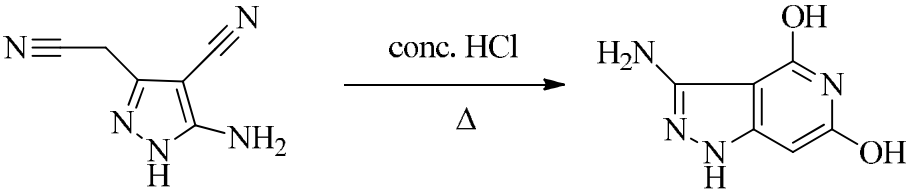
(3) (1)

The mechanism of reaction for synthesis of pyrazole involves Michael addition in which hydrazine hydrate attacks the α,β-unsaturated system of malononitrile dimer as intermediate and cyclization to give pyrazole.

1.3. Reactions of 5-amino-3-(cyanomethyl) -1H-pyrazole-4-carbonitrile:

1.3.1. Acid hydrolysis.

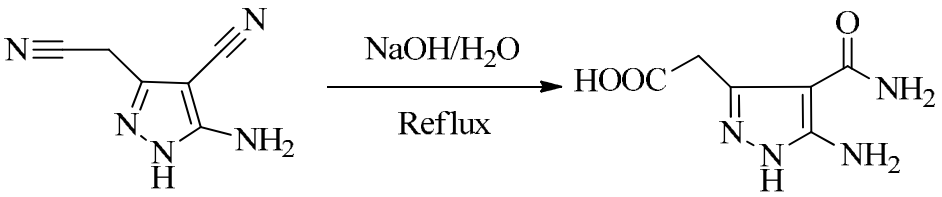
Hydrolysis of pyrazole involved conjugated nitrile group and non-conjugated nitrile group and can be occur in two medium, in the acid medium the hydrolysis of nonconjugated nitrile group to carboxylic acid and aromatic conjugated nitrile group to amide followed by cyclization and formed 3-amino-1H- pyrazolo[4,3-c]pyridine-4,6-diol[7,11] (4).



(1) (4)

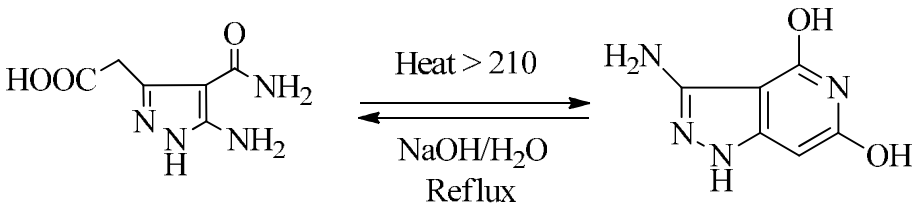
1.3.2. Alkaline hydrolysis.

Hydrolysis of pyrazole in base medium is more resistent to complete cyclization and formed 2-(5-amino-4-carbamoyl-1H-pyrazol-3-yl)acetic acid[7] (5).



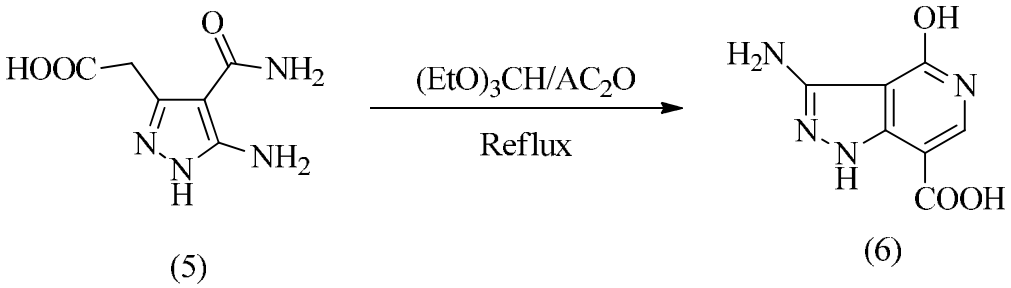
(1) (5)

Compound (5) could be reconverted to compound (4) by heating above its melting point.



(5) (4)

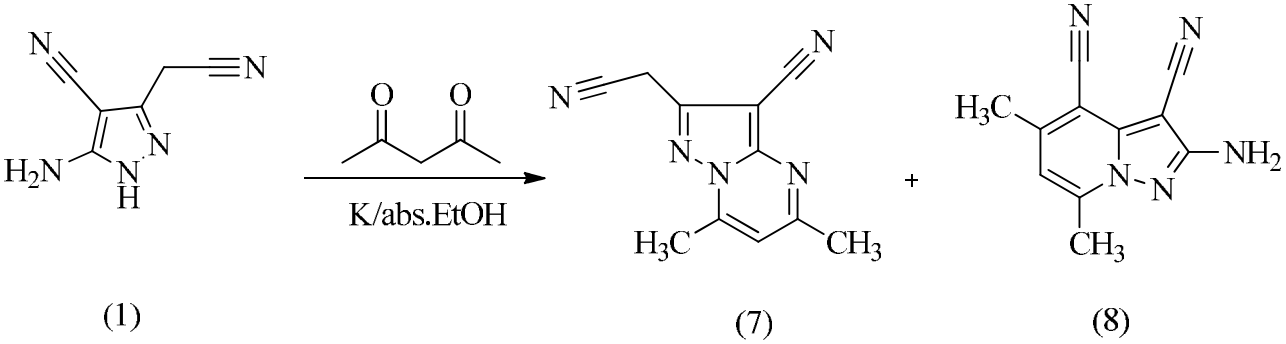
Reaction of compound (5) with a mixture of acetic anhydride and triethyl orthoformate gave 3-amino-4-hydroxy-1H-pyrazolo[4,3-c]pyridine-7-carboxylic acid (6).



(5) (6)

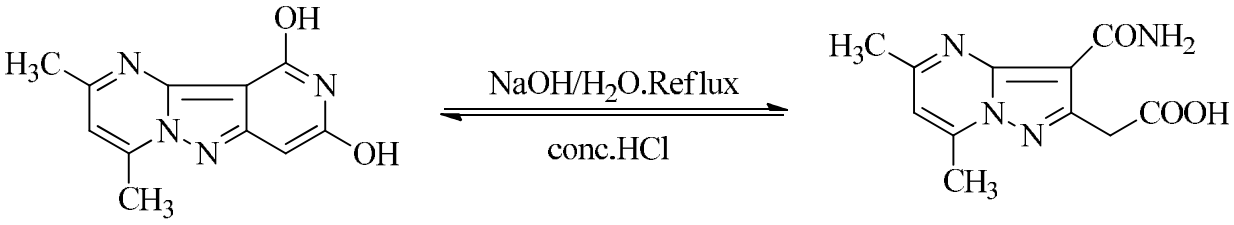
1.3.3. Reaction with pentane-2,4-dione.

The reaction yielded two isomeric products, the condensation of free amino group in compound (1) and carbonyl group in acetylacetone in the presence of potassium ethoxide followed by cyclization formed 2-(cyanomethyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3 carbonitrile (7), also the condensation of active methylene group in compound (1) with carbonyl group of acetylacetone followed by cyclization yielded 2-amino-5,7-dimethylpyrazolo[1,5-a]pyridine-3,4-dicarbonitrile[7] (8).



(1) (7) (8)

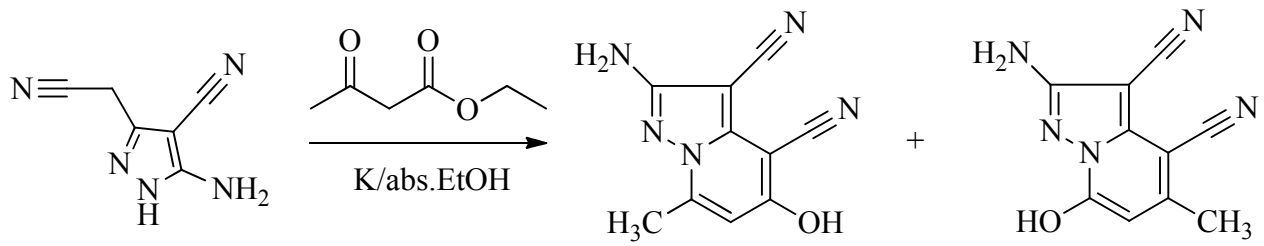
Hydrolysis of (7) in acid medium formed 2,4-dimethylpyrido[4,3:3,4]pyrazolo[1,5-a]pyrimidine-8,10-diol (9), which by alkaline hydrolysis form 2-(3-carbamoyl-5,7-dimethylpyrazolo[1,5-a]pyrimidin-2-yl)acetic acid (10), that could also be prepared by direct alkaline hydrolysis of compound (7).



(9) (10)

1.3.4. Reaction with ethyl-3-oxobutanoate.

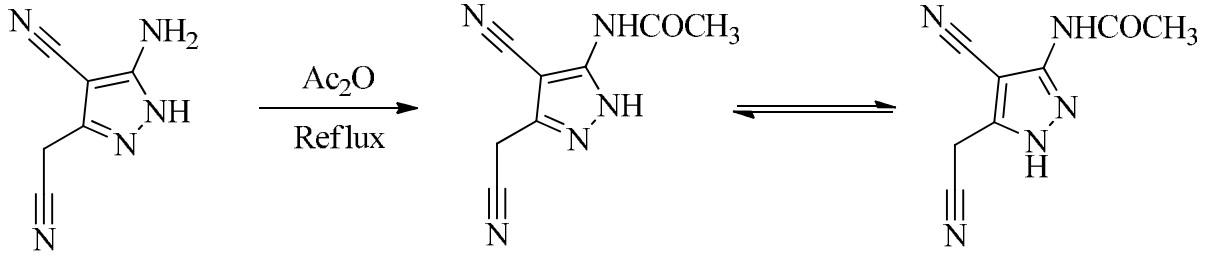
condensation of pyrazole with ethyl acetoacetate yielded one product 2-amino-5-hydroxy-7-methylpyrazolo[1,5-a]pyridine-3,4-dicarbonitrile (11) or 2-amino-7-hydroxy-5-methylpyrazolo[1,5-a]pyridine-3,4-dicarbonitrile (12), but no attempt to distinguish between these compounds[7].



(1) (11) (12)

1.3.5. Reaction with acetic anhydride.

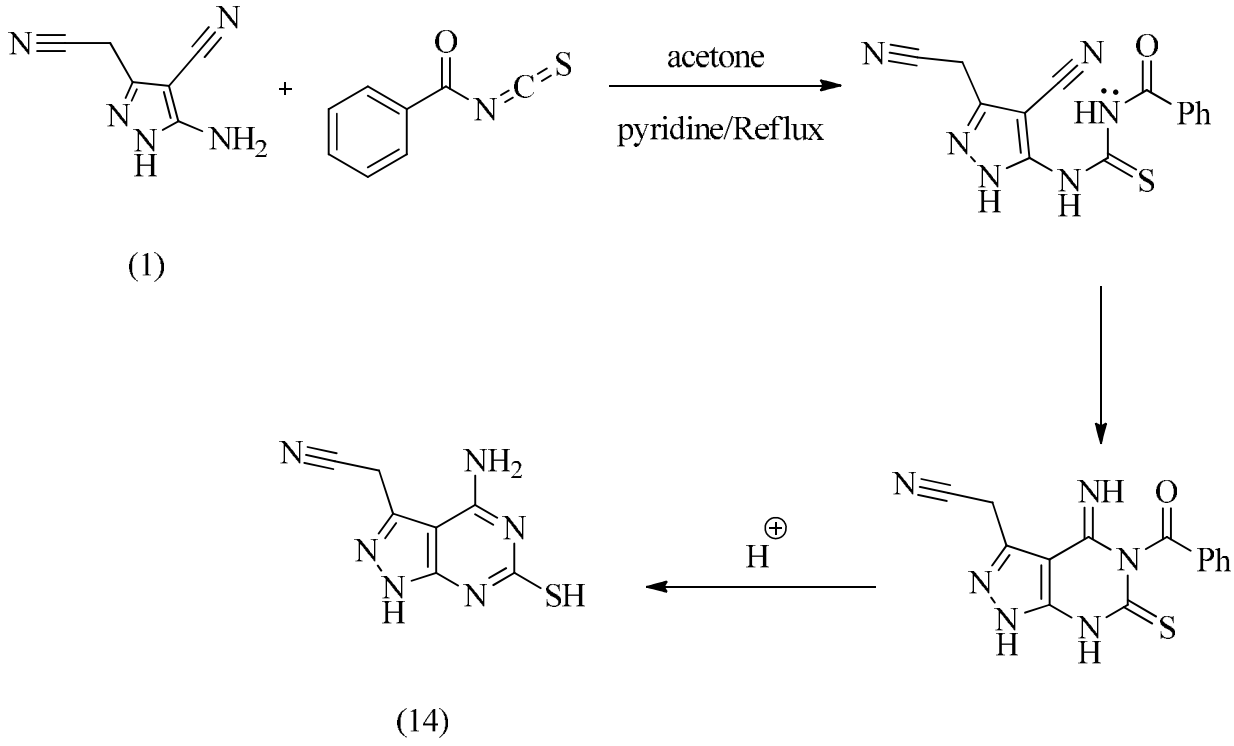
Acetylation of the amino group of pyrazole with acetic anhydride yielded in 90٪ N-(4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)acetamide (13a) in a tautomeric equilibrium with (13b)[7,13].



(I) (13a) (13b)

1.3.6. Reaction with benzoyl isothiocyanate.

Taylor and Elnagdi reported that the reaction of pyrazole with benzoyl isothiocyanate afford 2-(4-amino-6-mercapto-1H-pyrazolo[3,4-d]pyrimidin-3- yl)acetonitrile (14), the formation of the compound (14) proposed via cyclization of the benzoyl thiourea derivetive, where was intermediate formation through the reaction[14,15].

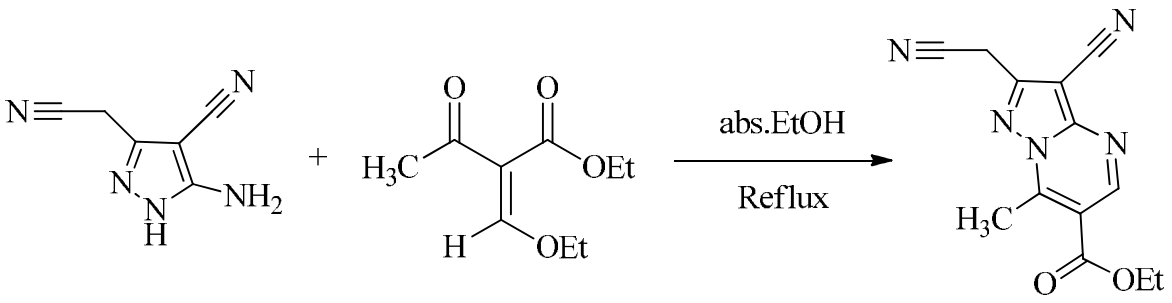


(1)

(14)

1.3.7. Reaction with ethyl 2-(ethoxymethylene)-3-oxobutanoate.

Refluxing of pyrazole with ethyl 2-(ethoxymethylene)-3-oxobutanoate in absolute ethanol give ethyl 3-cyano-2-(cyanomethyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate (15) by Michael addition followed by electrophilic attack of NH group of pyrazole ring on the carbonyl of acetyl group[16].

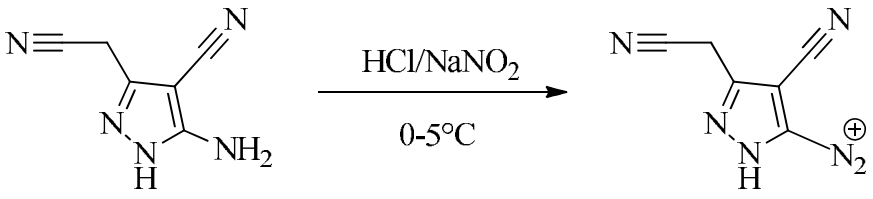


(1) (15)

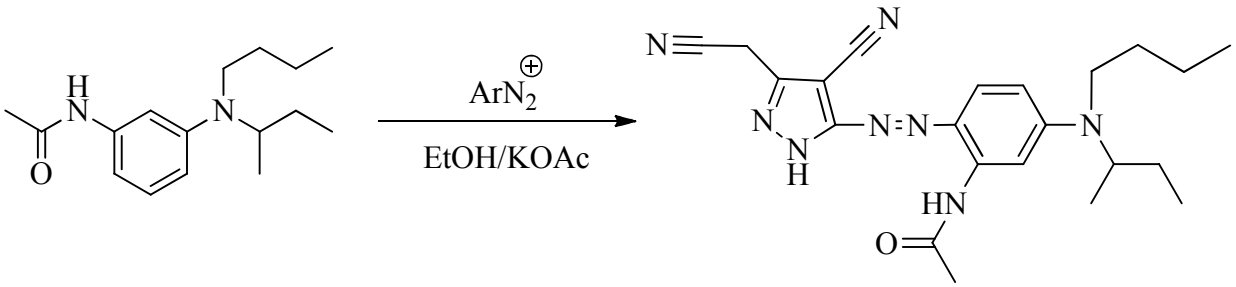
1.3.8. Reaction with nitrous acid.

Pyrazole has active aromatic primary amino group could be diazotize and couple with active methylene compounds and different aromatic compounds, which act as a nucleophilic center and attack the diazonium salt of pyrazole, that lead to formation of azo dyes.

Dye of N-(5-(sec-butyl(butyl)amino)-2-((4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)diazenyl)acetamide (16) may be prepared by diazotising pyrazole with nitrous acid, where formed unisolated diazonium salt of pyrazole[12].

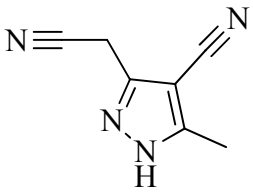


Immediately couple with N-(3-(secbutyl(butyl)amino)phenyl) acetamide in alkaline conditios.



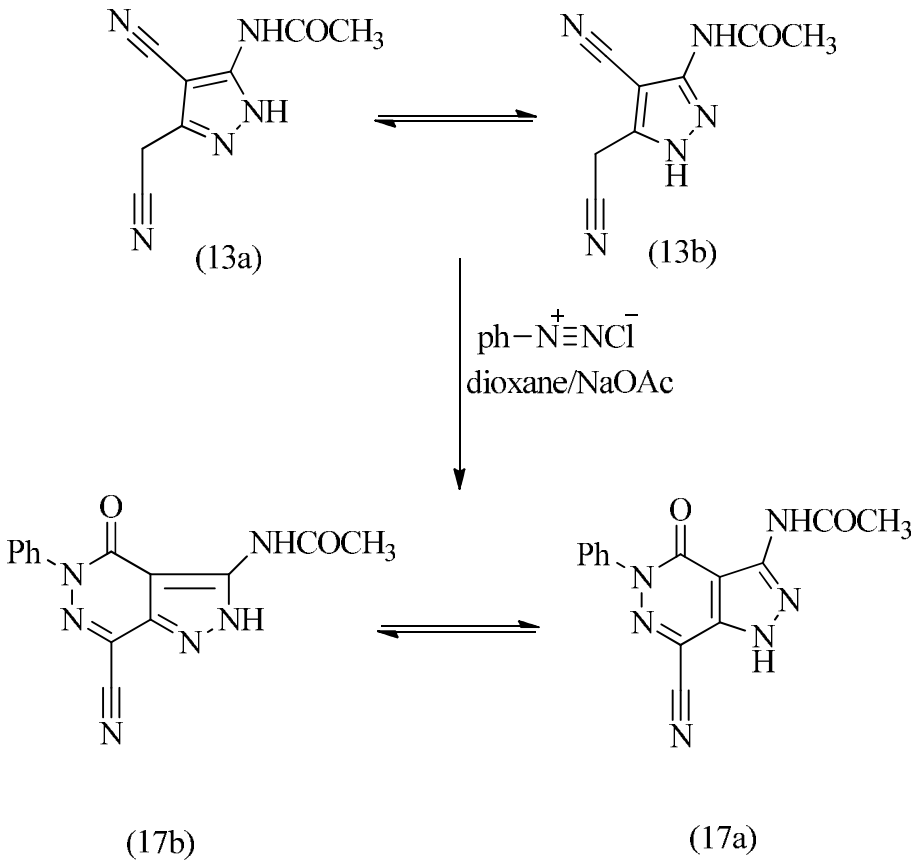
(16)

Ar=



On the other hand the pyrazole can be azo dyes through the active methylene group of the compound where couple with different diazonium salts.

Acetylation of pyrazole and coupling with benzenediazonium chloride afforded a tautomeric equilibrium mixture of N-(7-cyano-4-oxo-5- phenyl-4.5-dihydro-1H-pyrazolo[3,4-d]pyridazin-3-yl)acetamide (17a) and N-(7-cyano-4-oxo-5- phenyl-4.5-dihydro-2H-pyrazolo[3,4-d]pyridazin-3-yl)acetamide[13] (17b), the reaction occur via cyclisation and addition of acetic acid as follows:



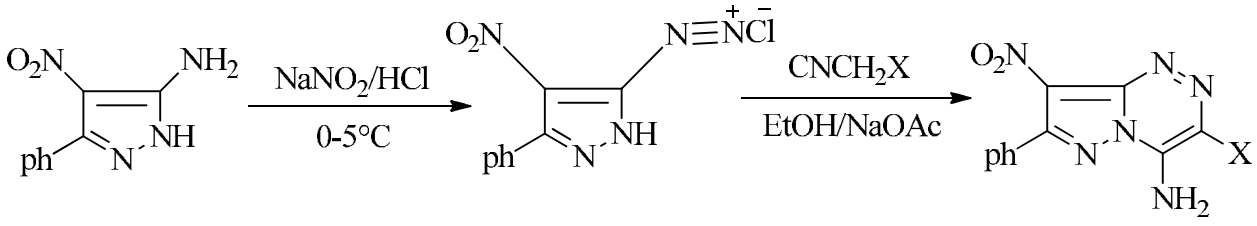
1.4. Azo dyes of Pyrazole derivatives.

Azo dyes are synthesized through two steps reactions diazotization and coupling, diazotization involves treating a primary aromatic amino group of pyrazole derivatives with nitrous acid to yield an aromatic diazonium ion, the next step is coupling of the diazonium salt of pyrazole derivatives with an nucleophilic compound in baseline conditions.

Active methylene compounds are very useful, where intermediate in organic synthesis, they show different reactions such as Knoevenagel condensation and synthesis of azo dyes, because of the acidic hydrogens in the active methylene group,

that could copulate with a number of amino aromatic compounds to configure various hydrazones. diazonium salt of pyrazole derivatives when coupled with active hydrogen reagents mainly malononitrile, ethyl cyanoacetate, ethyl acetoacetate, acetylacetone, pyrazole derivatives and pyrazolones, yield the corresponding azo derivatives or lead to formation of the pyrazolo[1,5-c] as-triazines[17,18], via cyclocondensation reaction, that took place by nucleophilic attack of the cyclic nitrogen atom of pyrazole on the electrophilic group in active hydrogen reagents.

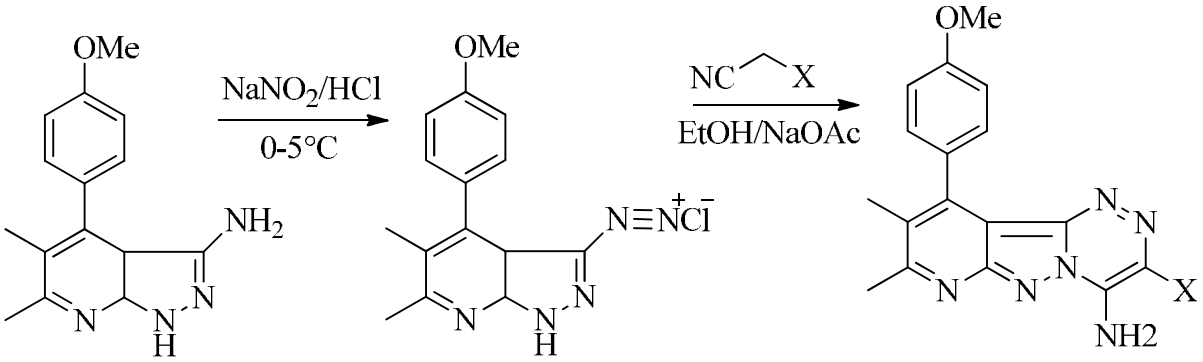
In 1989 where formed triazine derivatives directly under the same conditions of coupling reactions when 5-amino-3-phenyl-4-nitropyrazole (18) coupled with malononitrile and benzoylacetonitrile reagents, where readily cyclized to yield pyrazolo[5,1-*c*]-1,2,4-triazines (19a-b) respectively[19].



(18) (19a-b)

a,X= CN
b,X= COPh

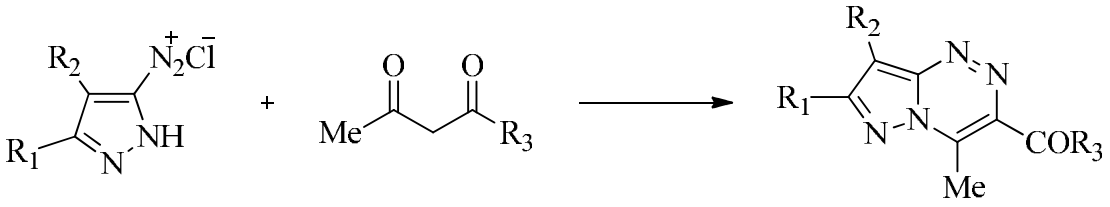
Also malononitrile reagent and benzoylacetonitrile reagent could easily coupled with the amino compound (20) and readily cyclized via stirring under the same conditions of coupling reaction to give (21a-b)[20] respectively as follows:



(20) (21a-b)

a,X= CN
b,X= COPh

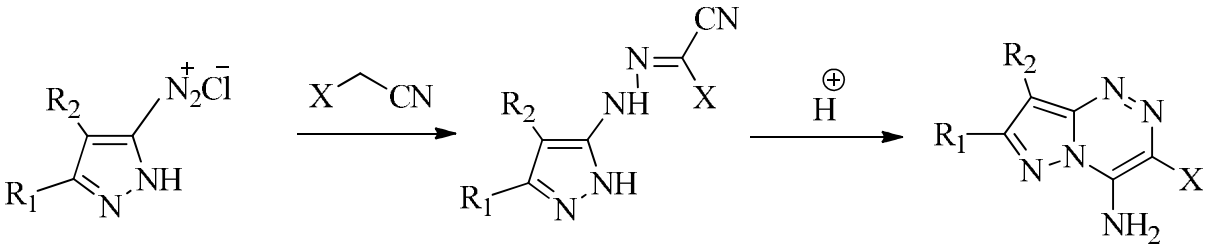
pyrazolyl diazonium chloride derivatives of compound (22) react with acetylacetone and ethyl acetoacetate and direct yield pyrazolo[5,1-c]1,2,4-triazines (23a-b)[4] respectively, via cyclocondensation reaction, which happened under coupling reaction conditions, that involve the endocyclic N atom and the exocyclic amino group in the compound as follows:



(22) (23a-b)

R_1, R_2 = H,alkyl,aryl
a,R_3=Me
b,R_3=OEt

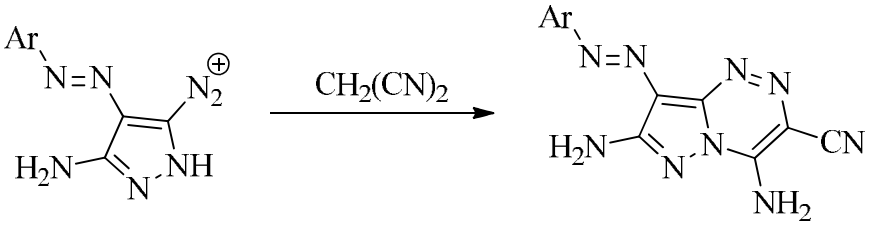
On the other hand pyrazolyl diazonium salts of compound (22) when coupled with a variety of active methylene reagents like malononitrile and ethyl cyanoacetate yielded 1H-pyrazol-5-yl-hydrazones (24a-b), that were readily cyclized in acid medium to pyrazolo[5,1-*c*]-1,2,4-triazines[4] (25a-b).



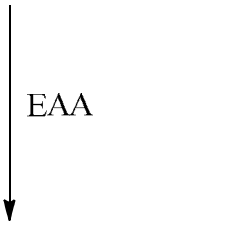
(22) (24a-b) (25a-b)

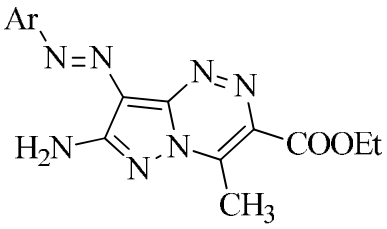
R_1, R_2 = H,alkyl,aryl
a,X=CN
b,X=CO_2Et

Diazonium salt of arylazopyrazole (26) coupled with malononitrile and ethyl acetoacetate yielded directly the pyrazolo[5,1-c]1,2,4-triazines[21] (27) and (28).

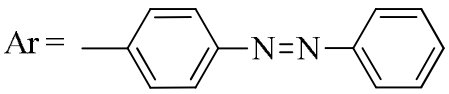


(26) (27)

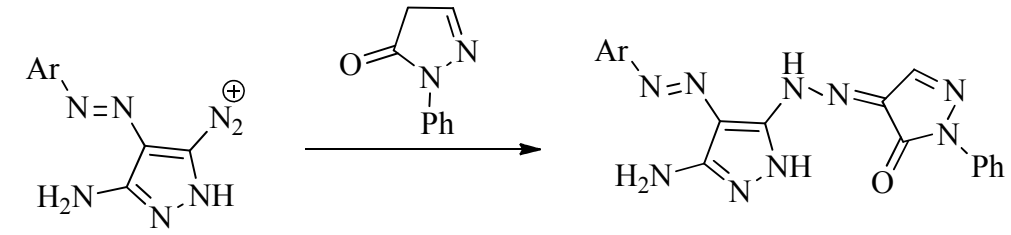




(28)



Attempts of cyclisation of compound (26) with N-phenyl pyrazolone and acetylacetone were unsuccessful, where afforded hydrazones (29) and (30).



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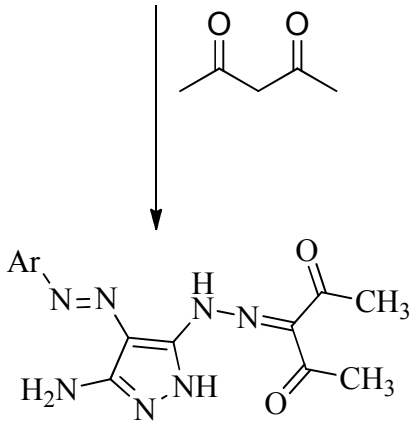
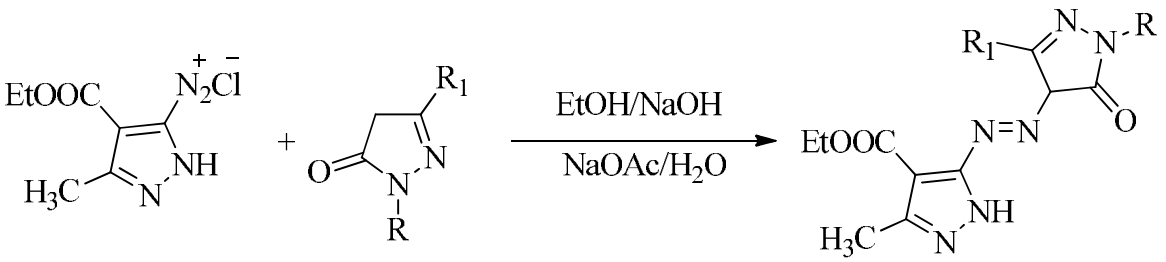


(30)

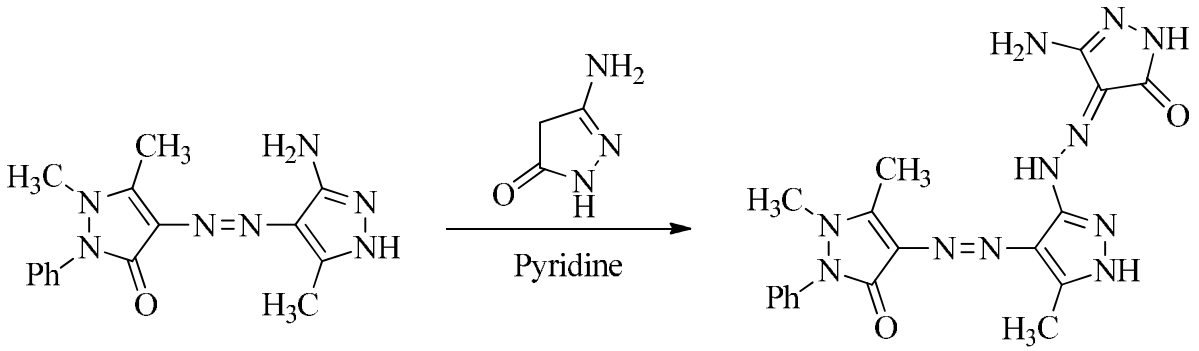
Diazotization of ethyl-5-amino -3-methyl-1H- pyrazole-4-carboxylate (31)[22], on reaction with mono and 1,3-disubstituted pyrazolones were formed three tautomeric forms of compounds (32a-c), as well as cyclization possibilities in good yield 85 ٪.



(31) (32a-c)

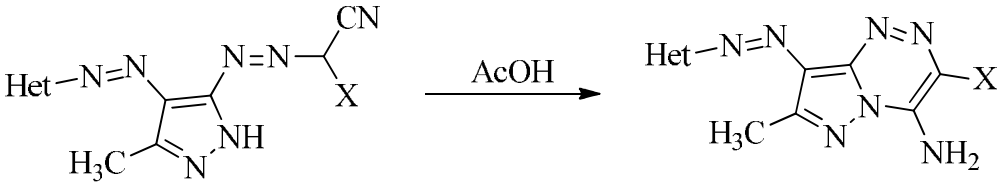
a,R=H,R_1=CH_3
b,R =p-C_6H_4-SO_3H,R_1=COOH
c,R=H,R_1=$COOC_2H_5$

Hydrazone derivative (34) were formed through conversion of 3-aminopyrazole (33) in to diazonium salts, followed by coupling with 3-amino-1H-pyrazol-5(4*H*)-one in pyridine[23].



(33) (34)

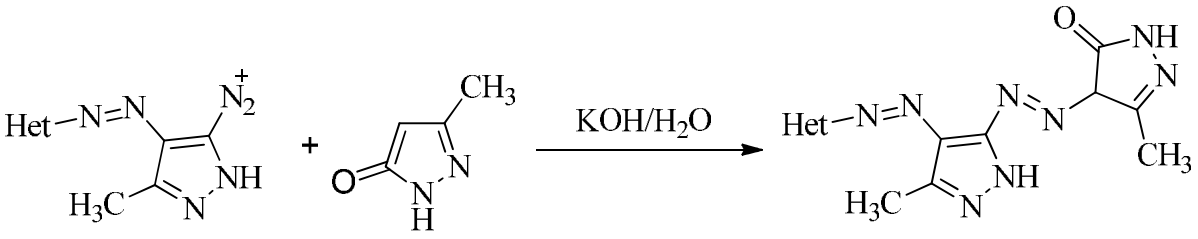
Karc[24] reported the ten novel pyrazolo[5,1-c][1,2,4]triazine dyes (36a-b), where synthesized by refluxing of pyrazolylazo malononitriles (35a) and ethyl pyrazolylazo cyanoacetate (35b) in glacial acetic acid.



(35a-b) (36a-b)

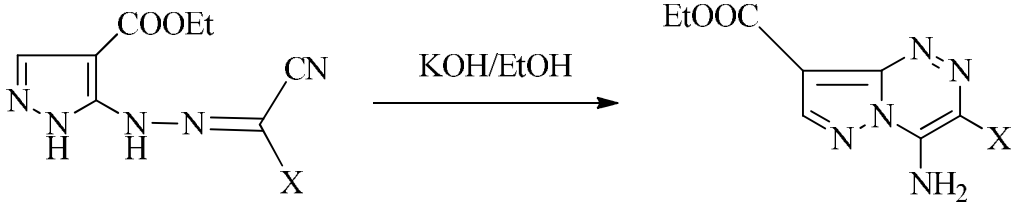
Het=Hetrocyclic compounds
a,X=CN
b,X=CO_2Et

whereas coupling reaction of 5-amino-3-methyl-4-hetarylazo-1H-pyrazoles (37) with 3-methyl-1H-pyrazole-5(4H)-one, produced pyrazolone dyes (38), without cyclize attempt[25] .



(37) (38)

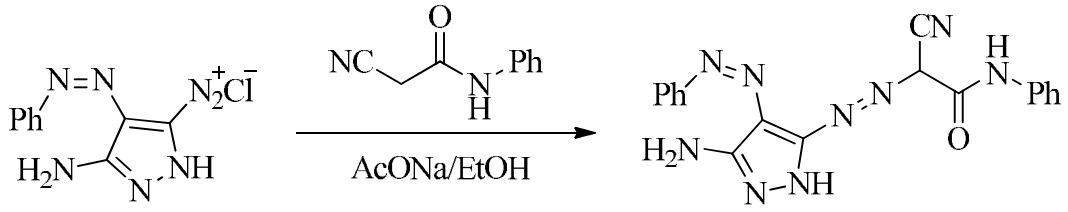
Refluxing of hydrazones (39a-c) with aqueous alcoholic potassium hydroxide solution afford ethyl-4-amino-3-substituted- pyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylates (40a-c) proposed via nucleophilic attack of the pyrazol NH on the cyano group[26].



(39a-c) (40a-c)

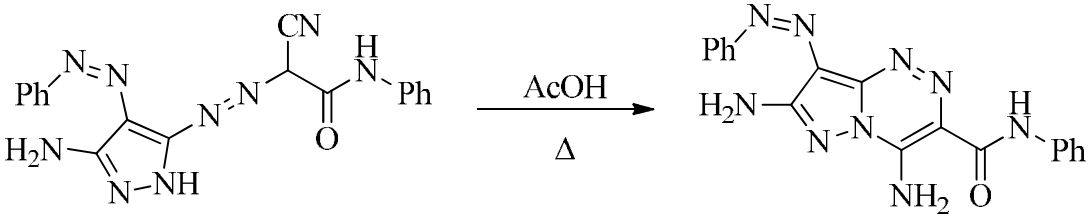
a,X=CN
b,X=CO_2Et
c,X=COPh

pyrazolyl diazonium chloride (41) have been coupled with the active methylene of cyanoacetanilide and afforded the corresponding hydrazone derivative (42)[27].



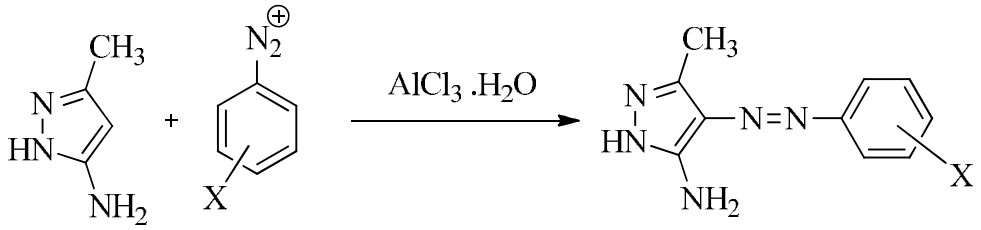
(41) (42)

Also cyclocondensation reaction be completed when compound (42) was refluxed with acetic acid. The reaction mechanism occur via nucleophilic attack of the ring nitrogen atom on the electrophilic cyano group in the compound to yield (43)[27].



(42) (43)

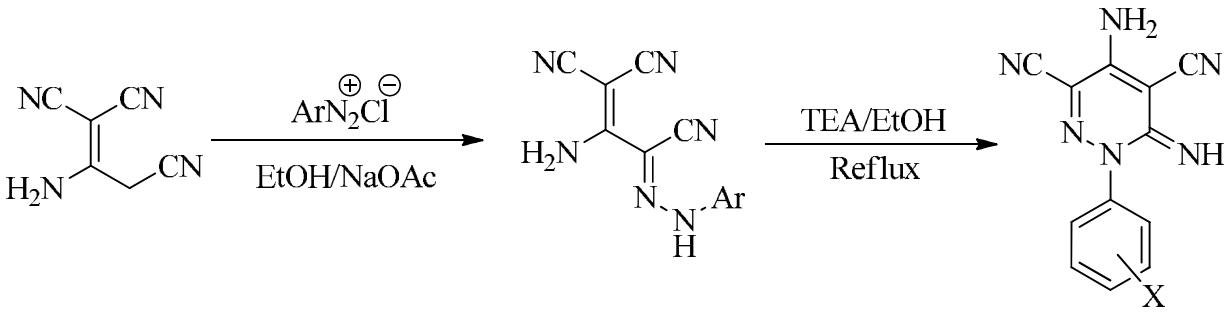
Diazocoupling reaction of anilines (44a-m) with 5-amino-3-methyl-1H-pyrazole in the present of $AlCl_3$ as the catalyst, proceed 5-amino-4-arylazo-3-methyl-1H-pyrazole derivatives (45a-m) in high yield[3].



(44a-m) (45a-m)

a,X=H
b,c,d,X= {p-o-m-OCH_3
e,f,g,X={p-o-m-CH_3}
h,i,j,X={p-o-m-NO_2}
k,l,m,X={p-o-m-Cl}

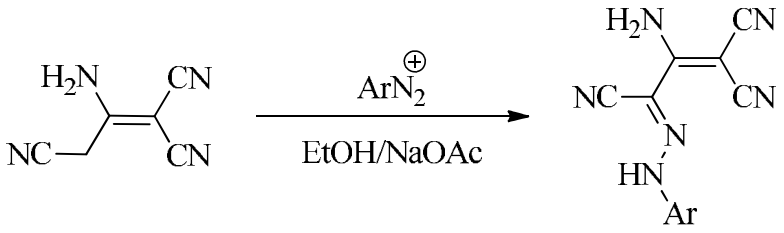
Malononitrile dimer reacted with different aryldiazonium chlorides to give pyridazine derivatives that were found to be a good intermediate for the formation of fused heterocyclic compounds[28]. The reaction of MND with diazonium chlorides salts of aniline derivatives yielded intermediate substituted arylhydrazones (46a-b), that readily cyclize in base medium to pyridazinimine derivatives (47a-b)[29,30].



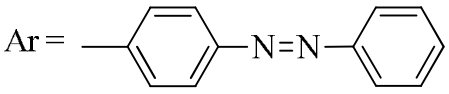
(46a-b) (47a-b)

a,X= m-OCH3
b,X=p-Cl

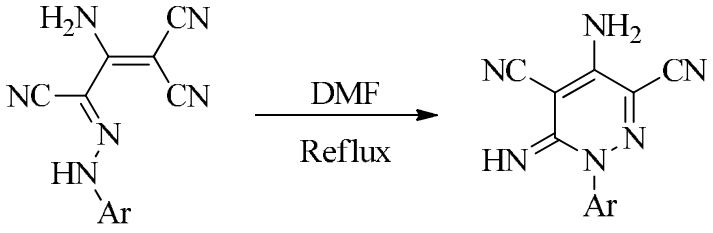
the mechanisum of reaction based on the addition of the hydrazo NH group to the cyano group in most reactions. also the coupling reaction of MND with diazonium salt of p-aminoazobenzene, afford arylhydrazone (48)[21].



(48)



that quickly converted to pyridazinimine derivative (49), when was boiled for a short period of time in DMF.



(48) (49)

Chapter Two

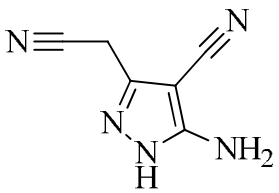
DISCUSSION

2.1. Discussion:

Diazotization of (5-Amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile) and diazo coupling in the presence of active methylene compounds exhibited a nucleophilic attack to yield azo dyes identical, dependent on the medium of reaction, sometimes there are several possibilities for the precipitation of products, depends on the value of the pH, and by experiences we have noticed that the best condition the precipitation of products in high yield be acidic or weak acidic medium through controlling the amount of acid and base added.

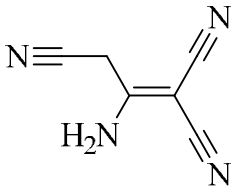
2.2. synthesis of pyrazole

Preparation of pyrazole was carried out using Taylor[7] procedure, proved melting point, IR which showed characteristic bands of amino group and nitrile groups also NMR spectrum showed signals of the amino groups which were identified by D_2O-exchange technique, the presence of deshielded singlet signal showed the appearance of methylene group, ^{13}CMR agree with all information obtained leading to the structure of (5-Amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile) as follows:



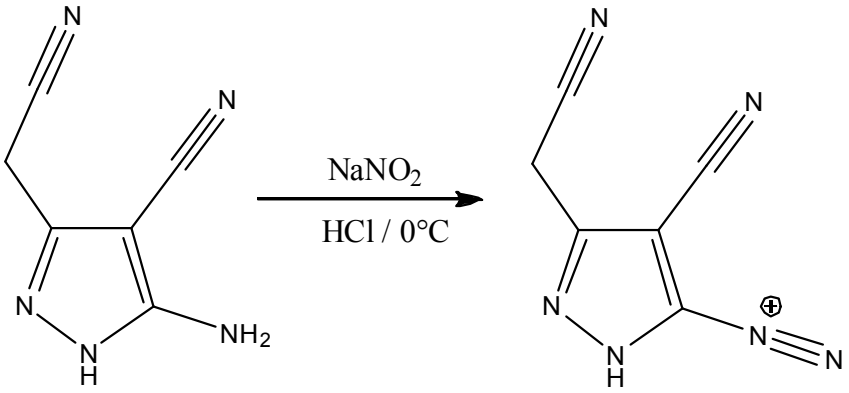
2.3. synthesis of malononitrile dimer

Chemic[9] procedure is a simple method for the dimerization of malononitrile, melting point, IR band at 3320 cm^{-1} refer to NH_2 group beside the appearance of CN bands at 2214 cm^{-1} and 2190 cm^{-1}. The NMR spectrum confirm that structure is 2-aminoprop-1-ene-1,1,3-tricarbonitrile due to the signals at 3.81 ppm for CH_2 and exchangeable NH_2 protons at 8.99 ppm.



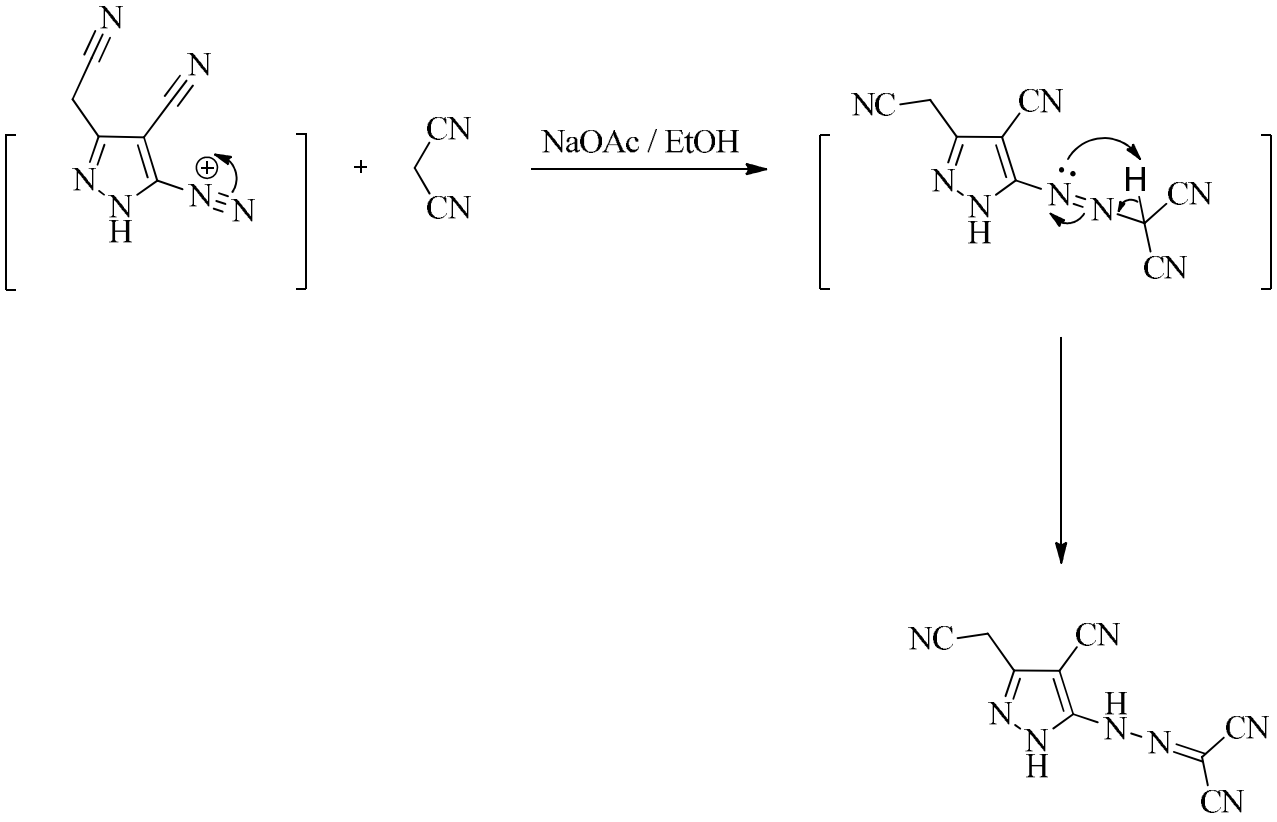
2.4. Diazotization of pyrazole

The first step the formation of diazonium salts of pyrazole, through treatment of pyrazole with nitrous acid (HNO_2), prepared from sodium nitrite ($NaNO_2$) and hydrochloric acid (HCl) at 0°C ,



2.5. synthesis of azo dyes of pyrazole

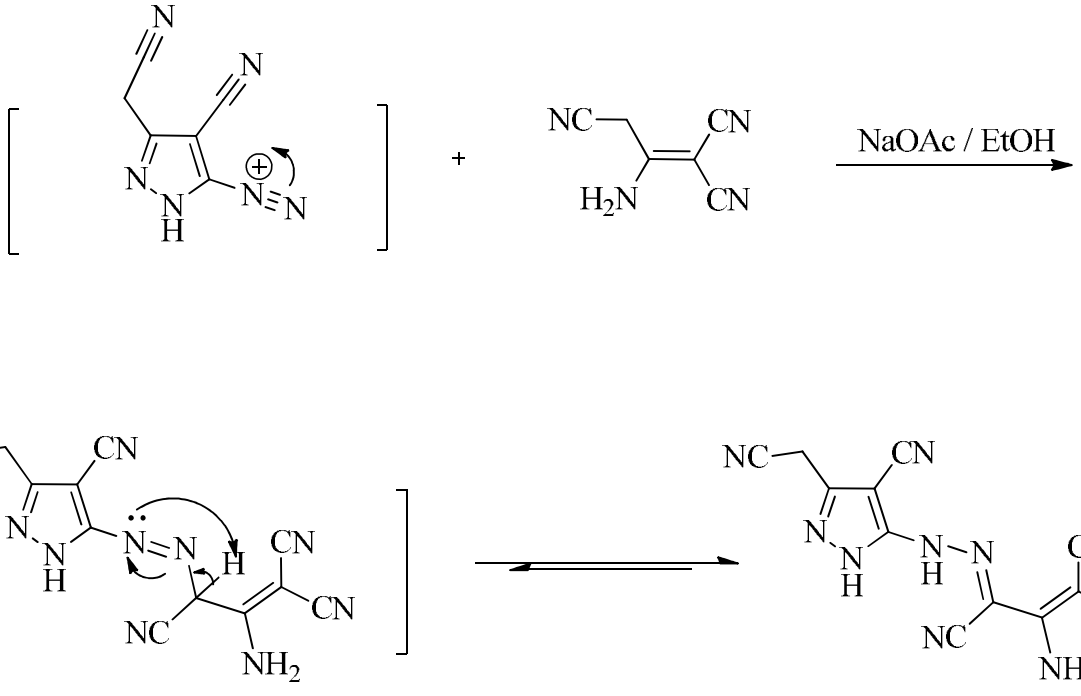
Malononitrile molecule is very active nucleophile, that can react with diazonium salt of pyrazole in good yield and quick coupling reaction, despite the difference of the value of the pH each time gives the same expected product (I) but in weak acidic was the best condition.



The structure of the obtained products were confirmed by satisfactory spectroscopic analysis ^{1}H-NMR spectra show three different types of protons, the amino group of

pyrazole has been disappeared and appear a singlet signal of NH at chemical shift ranging from 4.42 – 4.55 ppm which was proved by D_2O exchange . Also carbon magnetic resonance spectrum showed signals at 112.21 and 112.66 ppm indicating appeared conjugate cyano groups in addition to another cyano groups of pyrazole.

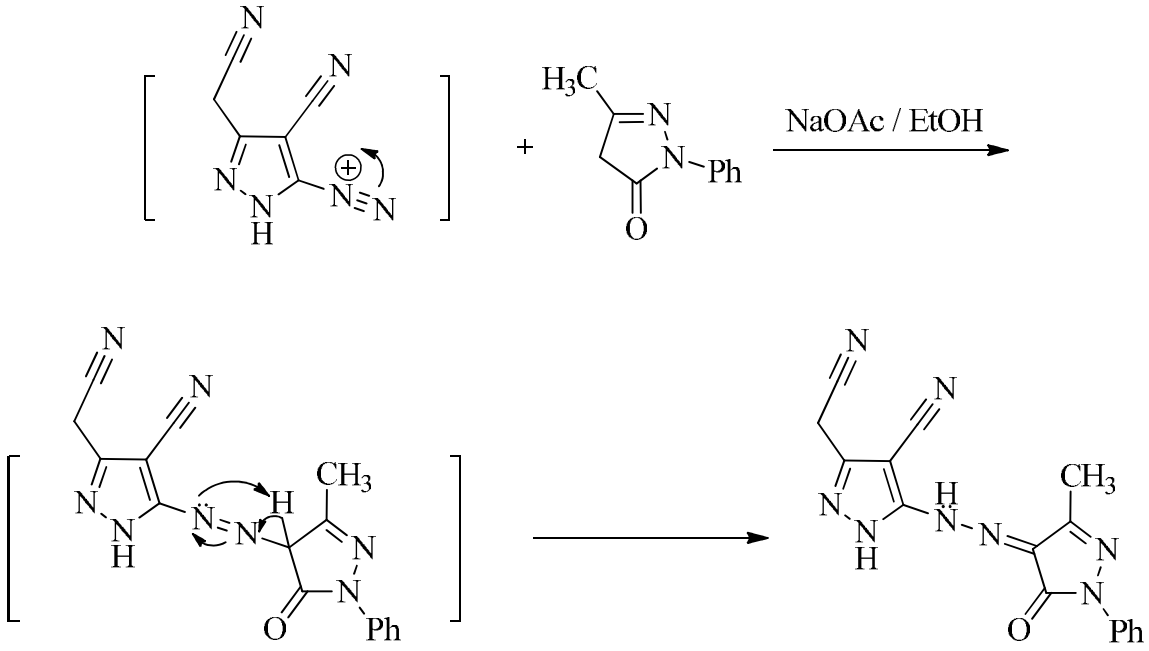
according to literature[21], the basic ethanolic solution of MND was very active toward coupling with the preformed pyrazolyldiazonium chloride in quick coupling reaction, where in the active methylene of MND is very active than the amino group to the nucleophilic addition so easy to reacte affording compound (II), despite the attempts changing the value of the pH each time gives the same expected product without possibility of cyclization, but in pH less than 1 was the best formed as yellowish crystals, as in the next reaction.



Compound (II) was confirmed by satisfactory spectroscopic analysis, the infra red spectrum showed strong bands at (2211- 2231 cm-^{1}) sign to the presence of corresponding conjugated cyano groups of dimer and conjugated cyano group of pyrazole, in addition to appearance of strong band of sp^2 at (3140 cm^{-1}) to confirm presence of CN double bond of the compound. H^1-NMR spectra showed appearance of the active methylene of pyrazole at 3.75 ppm that also confirmed by Dept spectroscopic technique where exhibit only one CH_2 at 17.63 ppm in absence of CH_2 of dimer sign to formation of CN double bond that was apparent in

^{13}C-NMR at signal 111.72 ppm, as well as cyano groups of the compound.

Reaction of pyrazole with 3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one depends on the alteration of value of the pH through the reaction, when the conditions of the reaction was changed at pH more than 5 the reaction gives a mixture of outputs (III) and (IV), therefore it was necessary to find a way to separate the outputs through controling of the rate of pH, in weak acidic medium the nucleophilic addition of the active methylene of the pyrazolone on the diazonium salt enable in attacking chance of NH and disappearing of methylene group of pyrazolone and formation of (III), according to the suggested mechanism as follows.

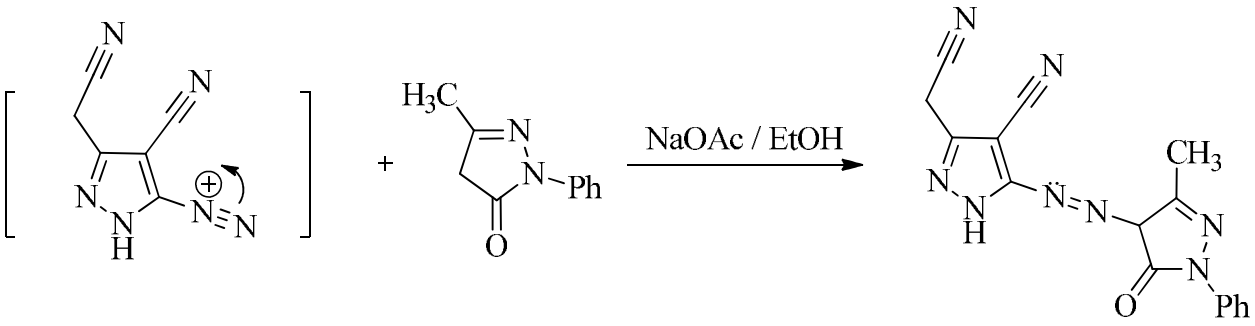


NMR informations were noted the absence of aliphatic protons of methylene groups of the pyrazolone ring which gave an idea that there is no NN double bond, also showed a sharp signal of NH are coincide at 4.23 ppm which was proved by D_2O exchange. In ^{13}C-NMR showed signals CH_3 and CH_2 at 12.18 & 15.87 ppm, while methylene of pyrazolone ring has been disappeared and appeared peak of CN double bond at 121.33 ppm the mentioned peak proved the coupling reaction.

DEPT spectroscopy technique established existence of CH_2& CH_3, as well as CH groups of benzene ring of pyrazolone.

on the other hand coupling reaction of the active methylene of the pyrazolone on the diazonium salt of pyrazole in pH less then 1 increase in attacking chance of the active

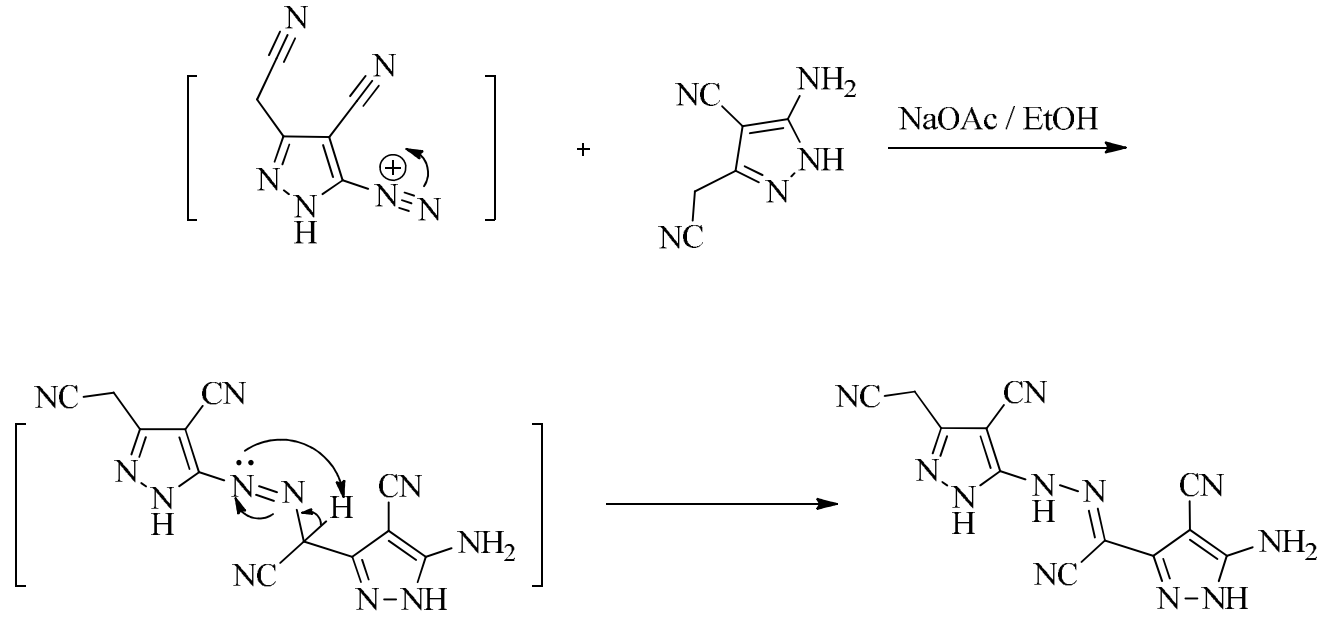
methylene and presence of NN double bond, leading to the actual product (IV) which is identified by comparison with the product (III) by M.P, TLC and by NMR spectroscopic analysis technique that gave characterstic mode of the obtained product according to mechanism in the following reaction.



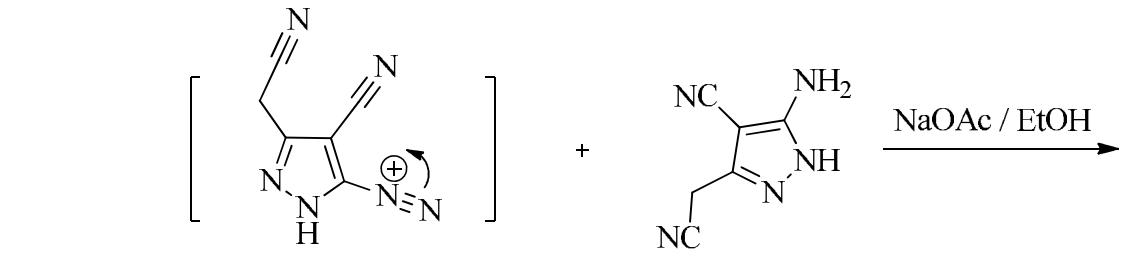
Compound (IV) showed additional singlet signal in H^1-NMR spectra represent the second proton of methylene group of pyrazolone ring at 2.39 ppm and disappearing of the signal of NH that indicated to presence of NN douple bond on comparison with the compound (III), also in ^{13}C-NMR spectra observations vanishing important signal of CN douple bond at 121.33 ppm.

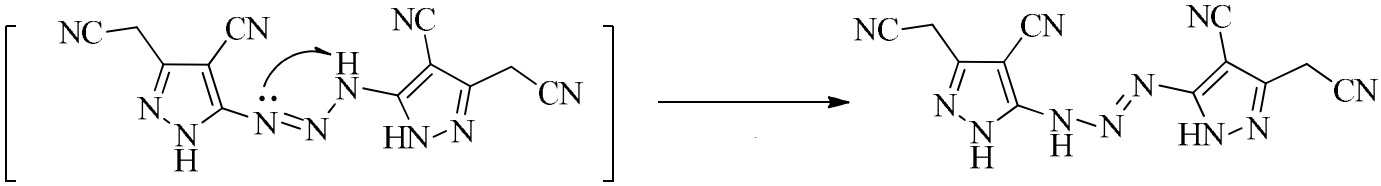
The active methylene group of the pyrazole has more nucleophilic character than the amino group to affording azo dyes in coupling reaction of pyrazole with its counterpart, where no yield was formed at pH less than 5, so the molecule of pyrazole was added followed by increase addition of anhydrous sodium acetate to activate the

nucleophilic attack of active methylene on diazonium salt to give nucleophilic adduct (V), suggested mechanism can be explained as following.



H^1-NMR spectra showed protons of the active methylene group as one singlet peak at 3.92 ppm, while the amino group is free appeared as signal at 6.43 ppm, as a reference to nucleophilic attack on the active methylene group of pyrazole and formation of CN double bond and this is confirmed by ^{13}C-NMR where showed just one signal of CH_2 at 16.98 ppm, also DEPT spectroscopic technique showed one signal of CH_2 nearly at 21.00 ppm.when the same reaction was carried out in specific conditions at pH less than 1the reaction can be explained through nucleophilic attack of nitrogen of pyrazole ring on diazonium salt where the actual product was (VI), which is identified by M.P, TLC and NMR spectroscopic analysis, the mechanism illustrated in the following mechanism.

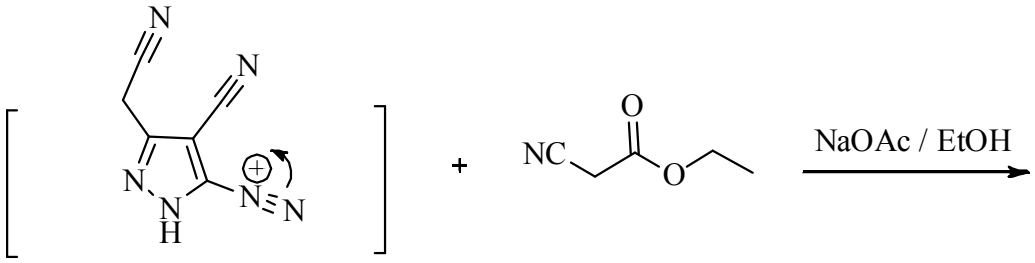


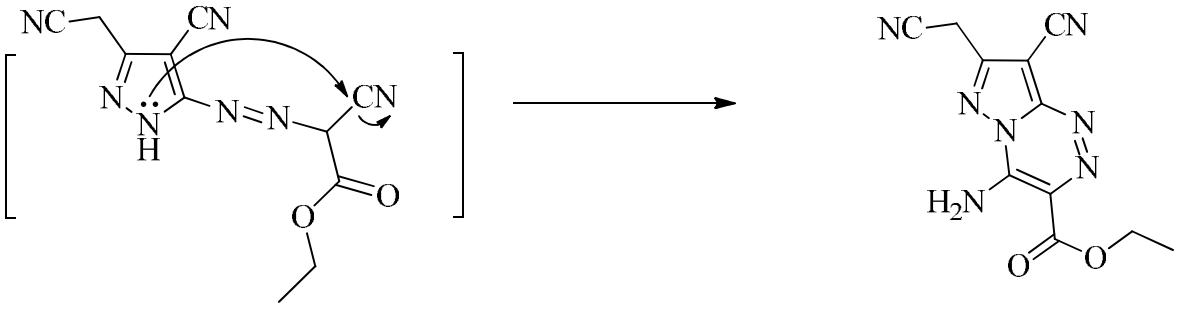


Where DEPT spectroscopy showed two signals of CH_2 of pyrazole rings at 16.72 ppm and 17.71 ppm which confirm formation of NN double bond instead of formation of CN double bond and also appear clear in ^{13}C-NMR where showed two signals of CH_2 at 16.72 ppm and 17.72 ppm, IR spectrum showed two strong absorption bands of conjugated cyano groups of pyrazole rings at 2225 cm^{-1} and 2239 cm^{-1} also there is a weak absorption band of NH appears at 3454 cm^{-1}.

as it is known from the literature[4,24] that the diazotization of pyrazole derivative and diazo coupling reaction in the presence of ethyl cyanoacetate exhibited a nucleophilic attack to yield azo dye identical that were directly readily cyclized in acidic medium to pyrazolo[5,1-c]-1,2,4-triazine (VII), proposed via nucleophilic attack of NH of the pyrazole on the conjugated cyano group, attempts of coupling reaction of pyrazole

with ethyle cyanoacetate to synthesis an identical hydrazone were unsuccessful although modification were applied, were formed the suggested structure (VII).

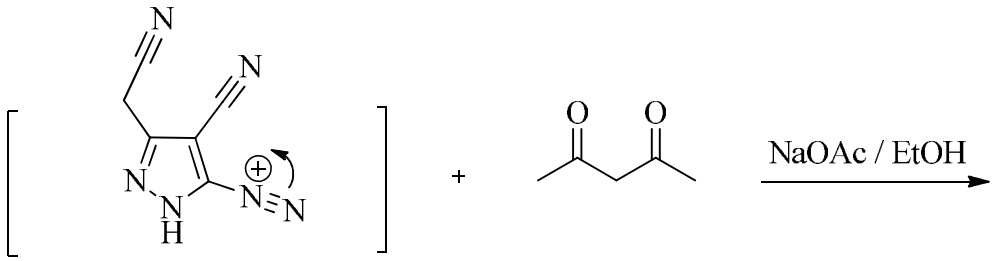


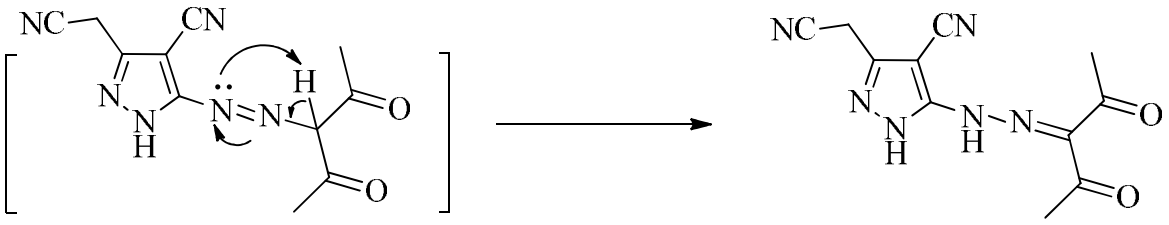


all the compounds obtained showed mostly the similar reaction features in creation of CN or NN double bond, in this reaction the formation of product can be explained through nucleophilic attack of nitrogen of pyrazole ring on the conjugated cyano group followed by cyclisation of the product, which confirmed by free amino group that appeared in H^1-NMR spectra as singlet signal at 4.67 ppm and that disappeared in D_2O exchange experiment, also disappearance of NH of pyrazole ring where showed mostly signal peak between 11-15 ppm, in addition to signal at chemical shift ranging from 1.33-1.46 ppm which is characteristic of methyl group, and signal at chemical

shift ranging from 4.23-4.33 ppm refer to methylene of carbonyl group that appear as clear signal in ^{13}C-NMR at 61.48 compared with methylene of pyrazole where showed a singlet at 16.93 ppm. DEPT spectroscopy analysis showed three variety of protons CH_3 and different two CH_2. IR spectrum showed strong absorption band of conjugated CN of pyrazole ring appear at 2228 cm^{-1}.

While pyrazolyldiazonium chloride have been coupled with the active methylene of acetylacetone and afforded the corresponding hydrazone (VIII), attempts of cyclisation of compound (VIII) via cyclocondensation reaction[4] which happen under coupling reaction conditions were unsuccessful where require specific conditions, despite the difference of the value of the pH each time gives the same expecting product as very weak yield but at weak acidic condition was the best condition to form the structure (VIII).





IR spectroscopic analysis gave characterstic mode of the obtained product where was clear appearance to carbonyl group of acetylacetone at 1714 cm^{-1}, in addition to conjugated cyano group of pyrazole ring that exhibit explaining the peak at 2231 cm^{-1}, ^{13}C-NMR spectra showed a signal at chemical shift ranging from 133.66-133.83 ppm that confirmed coupling reaction by appearance of CN double bond,

as well as methyl groups of acetylacetone that showed a singlet signal at chemical shift 25.89 ppm beside methylene group of pyrazole ring which showed a singlet signal at chemical shift 16.36 ppm, and that also in H^1NMR showed signals at chemical shift ranging from 3.80-3.92 ppm, H^1NMR showed signal at 12.62 ppm indicated the presence of NH of pyrazole ring and the disappearance in D_2O exchange experiment confirmed the expected product.

Chapter Three

EXPERIMENTAL

3.1. Experimental:

H^1-NMR

All the accurate analyzes of NMR were conducted in Micro-Analytical Unit at Cairo University, Proton magnetic resonance spectra were measured in hexadeutero dimethylsulfoxid (DMSO-d_6) solution, on Bruker 400 MHz

with chemical shift (δ) expressed in ppm down field from tetramethylsilane as an internal stander (δ MS=0). the multiplicity of the signal is as follow: s (Singlet), d (Doublet), t(Triplet), q(Quartet), m(Multiplet).

^{13}C-NMR

^{13}C-NMR were measured on Bruker 100 MHz with internal reference TMS δ=0, also measured by DEPT spectroscopy.

IR-Spectroscopy

the accurate analyzes of Infrared spectra were conducted in Omar El-Mukhtar University, where measured using FT-IR measurementsa Fourier transformer infrared FT-IR Spectro meter on Perkin Elmer model spectrum100, where the positions of absorptions have been expressed in wave number units (cm^{-1}).

Melting points

Melting points (m.p) of the synthesized compounds were measured in capillary tubes using stuart scientific apparatus and are uncorrected.

Chromatography

Analytical glass and aluminum plates were used with Kieselgel G or Kieselgel GF 254 (Merck). The plates were run in the following systems :

1- chloroform – methanol (different ratios).

2- chloroform – ethanol (different ratios).

3- ethyl acetate.

3.2. Solvents and Chemicals:

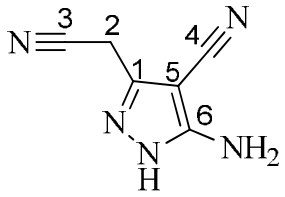
The following solvents and chemicals (research grade) were used as such in the present investigation.

Solvents and chemicals	Purity %	Company
Ethanol	99.9	MRS
Methanol	99.9	Fisher
Acetone	99.5	Loba
Diethyl ether	98	CDH
Ethyl acetate	99	T-Baker
Hydrochloric acid	37	Carlo-Erba
Sodium nitrite	98	Scharlau
Potasium hydroxide	85	Riedel-Dehaen
Sodium acetate anhydrous	98	BDH

Malononitrile	99	Aldrich
Ethyl cyanoacetate	98	Aldrich
Acetylacetone	puriss	Koch
1-phenyl-3-methyl-5-pyrazolone	98	Merck

3.3. synthesis of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile (1).

To a solution of (33.0 g, 0.5 mole) malononitrile in 85 ml of ethanol was added to 4.0 g of 85% hydrazine hydrateand the mixture was heated to boiling, then added 12.0 g of 85% hydrazine hydrate gradually, the reaction mixture continued to boil without external heating, noted the evaporation of ammonia strongly, after adding all amounts of hydrazine hydrate, the reaction mixture was boiled for an additional 5 minutes, then quickly cooled to 0 ^{0}C, and filtered immediately, recrystallized from glacial acetic acid and again of water, yielded the color-less needles of compound (I).



(1)

Yield:13.5g 37%

mp: 197-199^{0}C

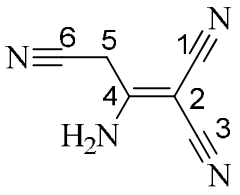
H^{1}-NMR:δ = 3.94 (2H, s, CH2), 6.48 (2H, s, exchangeable, NH_2),12.00 (H, s, exchangeable, NH).

^{13}C-NMR: δ = 16.75 ($1C_2$), 71.86 ($1C_5$), 114.80 ($1C_3$), 117.34 ($1C_4$), 143.77 ($1C_1$), 154.51 ($1C_6$).

IR: 3457, 3352, 3212, 2919, 2265, 2218, 1688, 1646, 1592, 1544 cm^{-1}.

3.4. Synthesis of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3).

To a cooled solution of (7g, 0.125mol) of potassium hydroxide in 50 ml of ethanol, was added (16.5 g, 0.25 mol) of malononitrile. after 5-10 mins under stirring and refluxing temperature the potassium salt of malononitrile dimer was precipitated. After 30 mins of refluxing the mixture is cooled, where collected by filtration and washed with cold ethanol and dried. The separated salt is dissolved in a small amount of water and acidifying with concentrated hydrochloric acid to pH 4, filtered off and recrystallized from water to yield colorless needles.



(3)

Yield:13.5g 82%

mp: 170-173^{0}C

H^{1}-NMR:δ = 3.81 (2H, s, CH_2), 8.99 (2H, s, exchangeable, NH_2).

^{13}C-NMR: δ = 22.64 ($1C_5$), 50.35 ($1C_2$), 114.68 ($1C_1$), 115.05 ($1C_3$), 115.81 ($1C_6$), 165.16 ($1C_4$).

IR:3320, 3196, 2214, 2190, 1619, 1503 cm^{-1}.

3.5. Synthesis of pyrazole azo dyes.

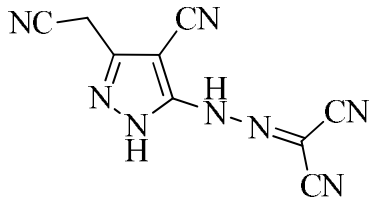
General procedure:

A mixture of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile (1) (0.01mole) in concentrated HCl (xml) was cooled to 0- 5 ^{o}C under ice, and cooled sodium nitrite solution (y mole) in water, added to it dropwise during ten minutes, the reaction mixture was stirred for one hour under ice, the clear diazonium salt solution was added dropwise to a well-cooled (0 - 5 ^{o}C) solution of active methylene compounds (0.01 mole) in an anhydrous sodium acetate (zmole) dissolved in (20 ml) of ethanol/methanol, stirring was continued for four hours, then been left about one hour at room temperature for precipitating, the separate products were filtered and washed with cold water several times then ethanol.

The table below shows the amounts of acid and base were added.

Quantities / Method	HCl	$NaNO_2$	CH_3COONa
A	3 ml	0.01mole in 3ml H_2O	0.015 mole
B	3 ml	0.02 mole in10 ml H_2O	0.05 mole
C	20 ml in 20 ml H_2O	0.02 mole in10 ml H_2O	0.05 mole
D	20 ml	0.02 mole in 10 ml H_2O	0.05 mole

3.5.1. (4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)carbonohydrazonoyl dicyanide (I).



Method: B

Yield:1.35g 60%

mp: 250-252^{0}C Dec

Mol.Formula:$C_9H_4N_8$(224)

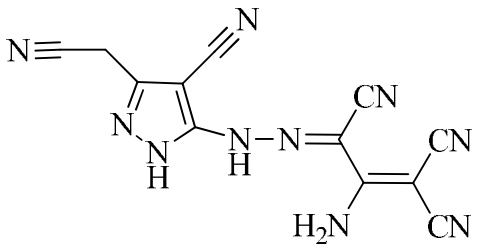
IR: 3312, 3174, 3319, 2948, 2236,1663,1587cm^{-1}

H^{1}-NMR:δ = 3.94 (2H, s, CH2), 4.48 (H, s, exchangeable, NH),10.30 (H, s, exchangeable, NH).

^{13}C-NMR: δ = 17.42 (1C), 81.14 (1C), 112.21 (1C), 112.66 (1C), 115.65 (1C), 116.30 (1C), 143.45 (1C), 151.11 (1C), 151.68 (1C).

C-Dept: 17.35(CH_2).

3.5.2. 2-amino-3,3-dicyano-N'-(4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)acrylohydrazonoyl cyanide(II).



Method: A

Yield:2.11g 73%

mp: 260-262^{0}C Dec

Mol.Formula: $C_{12}H_6N_{10}$(290)

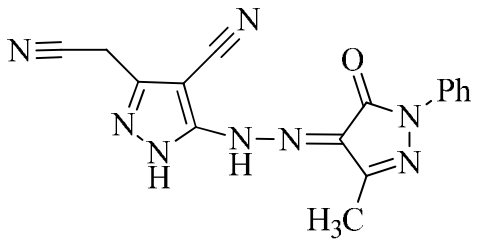
IR: 3441, 3320, 3193, 2961, 2220, 2206, 1616,1596cm^{-1}

H^1-NMR:δ = 3.75 (2H, s, CH2), 7.32 (2H, s, exchangeable, NH_2), 13.20 (H, s, exchangeable, NH).

^{13}C-NMR:δ = 16.21 (1C), 77.55 (1C), 111.72 (1C), 112.98 (1C), 115.03 (1C), 115.97 (1C), 116.55 (1C), 116.83 (1C), 144.01 (1C), 156.14 (1C), 162.01 (1C).

C-Dept: 17.63(CH_2).

3.5.3. 3-(cyanomethyl)-5-(2-(3-methyl-5-oxo-1-phenyl-1H-pyrazol-4(5H)-ylidene)hydrazinyl)-1H-pyrazole-4-carbonitrile (III).



Method: C

Yield:1.77g 53%

mp:280-283^{0}C Dec

Mol.Formula:$C_{16}H_{12}N_8O$ (332)

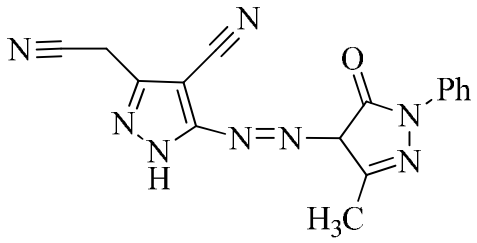
IR:3189, 2228, 1705, 1595 cm^{-1}

H^1-NMR: δ = 2.18 (3H, s, CH_3), 3.90 (2H, s, CH_2), 7.13-7.79 (5H aromatic), 4.23 (H, s, exchangeable, NH),13.00 (H, s, exchangeable, NH).

^{13}C-NMR: δ = 12.18 (1C), 15.87 (1C), 113.04 (1C), 116.36 (1C), 118.26 (2C), 121.33 (1C), 125.54 (1C), (1C), 129.57 (2C), 138.27 (1C), 149.30(1C), 156.63(2C).

C-Dept: 16.50(CH_3), 20.00 (CH_2),122.5(2CH), 129(CH), 134(2CH).

3.5.4. 3-(cyanomethyl)-5-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)-1H-pyrazole-4-carbonitrile (IV).



Method: A

Yield:1.82g 55%

mp: 279-281 ^{0}C Dec

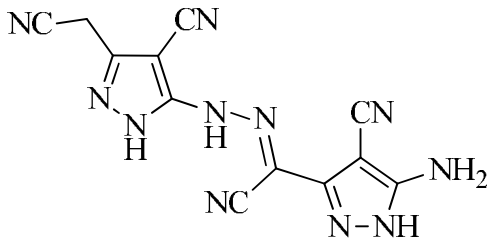
Mol.Formula:$C_{16}H_{12}N_8O$ (332)

H^1-NMR:δ = 2.22 (3H, s, CH_3), 2.39 (H, s, CH), 3.76 (2H, s, CH_2), 7.22-7.80 (5H aromatic), 14.58 (H, s, exchangeable, NH).

^{13}C-NMR:δ = 12.18 (1C), 15.87 (1C), 113.04 (1C), 116.36 (1C), 118.26 (2C), 121.33 (1C), 125.54 (1C), (1C), 129.57 (2C), 138.27 (1C), 149.30(1C), 156.63(2C).

C-Dept: 16.50(CH_3), 20.00 (CH_2),122.5(2CH), 129(CH), 134(2CH).

3.5.5. (Z)-5-amino-4-cyano-N'-(4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)-1H-pyrazole-3-carbohydrazonoyl cyanide (V).



Method: C

Yield:2.22g 73%

mp:200-220^{0}C Dec

Mol.Formula:$C_{12}H_7N_{11}$(305)

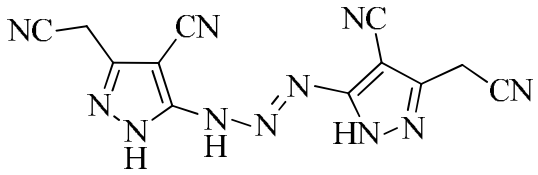
IR:3445, 3416, 3319, 2940, 2230, 2212, 1623, 1586cm^{-1}.

H^1-NMR: δ = 3.92 (2H, s,CH_2), 6.43 (2H, s, exchangeable, NH_2), 11.97(3H, s, exchangeable, NH).

^{13}C-NMR:δ =16.98 (1C), 72.00 (2C), 110.68 (1C), 114.98 (1C), 117.51 (1C), 121.28 (1C), 131.00 (1C), 143.98 (2C), 154.76 (2C).

Dept: δ = 21.00 (CH_2)

3.5.6. (E)-5,5(triaz-1-ene-1,3-diyl)bis(3-(cyanomethyl)-1H-pyrazol-4-carbonitrile (VI).



Method: D

Yield:1.98g65%

mp: 210-230^{0}C Dec

Mol.Formula:$C_{12}H_7N_{11}$(305)

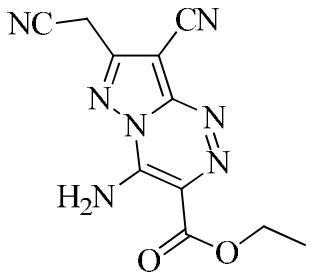
IR: 3454, 3157, 3089, 2926, 2239, 2225, 1620,1563cm^{-1}

H^{1}-NMR: δ = 3.94 (2H, s,CH_2).

^{13}C-NMR:δ = 16.72 (1C), 17.72 (1C), 114.15 (2C), 118.02(1C), 118.45 (1C).

Dept: δ = 16.72(CH_2), 17.72(CH_2).

3.5.7. ethyl-4-amino-8-cyano-7-(cyanomethyl)pyrazolo[5,1-c][1,2,4]triazines-3-carboxylate (VII).



Method: A

Yield: 2g 74%

mp: 175-177^{0}C Dec

Mol.Formula:$C_{11}H_9N_7O_2$ (271)

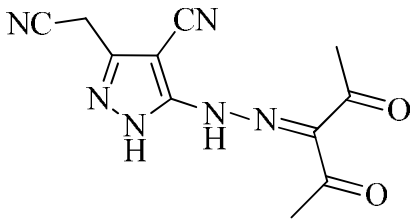
IR: 3262, 2973, 2900, 2228, 1683, 1618,1554cm^{-1}

H^1-NMR:δ =1.29 (3H, t, CH_3), 3.88 (2H, s, CH_2), 4.28 (2H, q, CH_2), 4.67 (2H, s, exchangeable, NH_2).

^{13}C-NMR:δ = 14.09 (1C), 16.93 (1C), 61.48 (1C), 141.54 (1C).

C-Dept: 14.51 (CH_3), 18.04(CH_2), 62.20(CH_2).

3.5.8. 3-(cyanomethyl)-5-(2-(2,4-dioxopentan-3-ylidene)hydrazinyl)-1H-pyrazole-4-carbonitrile (VIII).



Method: B

Yield: 1.58g 61%

mp: 185- 187^{0}C Dec

Mol.Formula:$C_{11}H_{10}N_6O_2$ (258)

IR: 3203, 2940, 2231, 2162, 1714,1624, 1559 cm^{-1}

H^1-NMR:δ = 2.45 (6H, s,2CH_3), 3.80&3.92 (2H, s,CH_2), 7.20 (H, s, exchangeable, NH), 12.62(H, s, exchangeable, NH_2).

^{13}C-NMR:δ = 16.36 (1C), 25.89 (2C), 73.24 (1C), 110.23 (1C), 120.67 (1C), 133.74 (1C), 143.10 (1C), 149.25 (1C).

Chapter Four

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Faculty of science
Department of chemistry

تكوين اصباغ الآزو لمركب البيرازول

A thesis submitted as partial fulfillment for the requirements of the degree of Master of Science in chemistry

By

Entesar M. El-OBIDE

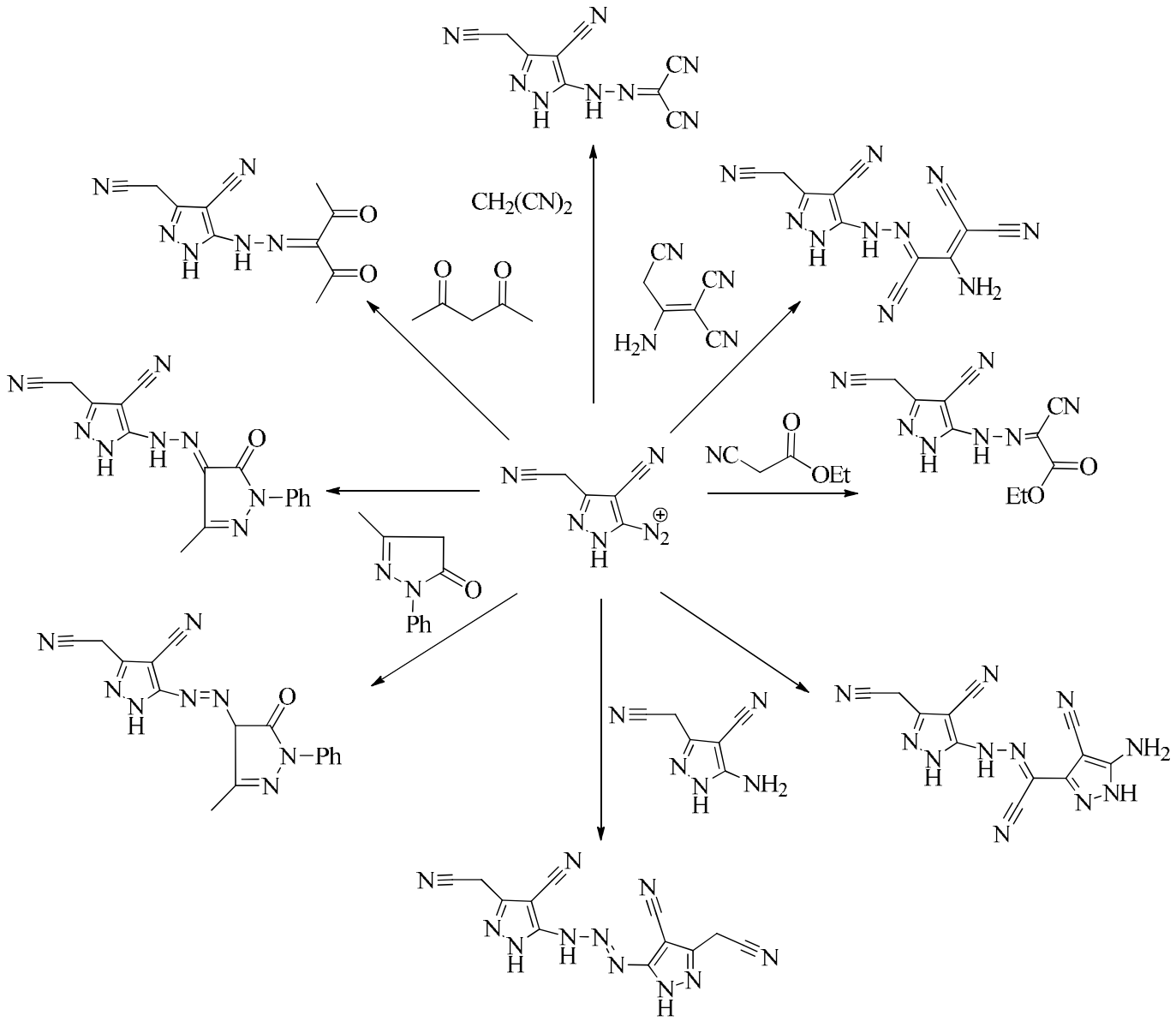
Supervisor

Prof. Dr. Abdalla H. Gheath

2015

الخلاصة

تم في هذا البحث تكوين آملاح الديازونيوم للمركب (5-امينو-3-سيانوميثيل-1-اتش بيرازول-4-كاربونيتريل) بواسطة تفاعل المركب مع حمض الهيدروكلوريك ونيتريت الصوديوم تحت درجة صفر درجة مئوية, املآح الديازونيوم الناتجة تتفاعل مع مركبات مختلفة تحتوي علي مجموعة الميثيلين النشطة في وجود اسيتات الصوديوم والايثانول, حيث تتفاعل كمركز نيوكلوفيلي وتهاجم املآح الديازونيوم لمركب البيرازول وتنتج اصباغ الآزو المماثلة. معدل التغير في تركيز ايون الهيدروجين يؤثر في تكوين اصباغ الآزو, حيث تفاعل الازدواج لمركب البيرازول مع مالونونيتريل وايثيل سيانو اسيتات واسيتيل اسيتون و (3,1,1-ثلاثي سيانو-2-امينو-1-بروبين) في وجود اسيتات الصوديوم كمنظم تفاعل يعطي كل مرة النواتج المتوقعة, بينما يكون هناك عدة احتمالات لترسيب النواتج وفقآ لمعدل التغير في تركيزايون الهيدروجين خلال تفاعل ازدواج املآح الديازونيوم لمركب البيرازول مع 3-ميثيل-1-فينيل-1اتش-بيرازول-5(4اتش)-اون, وتفاعل ازدواج مركب البيرازول مع جزئ بيرازول اخر.


CH2(CN)2