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Synthesis of Pyrazole Dyes Derivatives

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ABSTRACT

Eight azo dyes were prepared by diazotization of 5-amino-3 (cyanomethyl)-1H- pyrazole-4-carbonitrile in presence of sodium nitrite and hydrochloric acid at 0˚C. We reported that the malononitrile molecule was a very active nucleophile, where can react with the diazonium salt of pyrazole in presence of sodium acetate and ethanol to yield corresponding azo dyes of pyrazole. The dyes were characterized by elemental analysis and spectral methods. In addition, the effect of the pH value on the products yield of the dyes was reported.

1. Introduction

Pyrazole derivatives are important intermediates that possess biological and pharmacological activities (Karcı, F. 2008). Some azopyrazole derivatives also find application in dyes and complexes (Abdel-Latif, S.A. 2001). In this study, the synthesis of some azo dyes of pyrazole starting by diazotization of (5-Amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile) undergo a coupling reaction with malononitrile to generate the hydrazones (Popil'nichenko, S. 2005) in the presence of active methylene compounds exhibited a nucleophilic attack to yield identical azo dyes, depends on the pH value, 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. Experimental

2.1. General

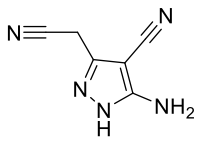
The Chemical analysis were used in the identification of the organic compounds. Nuclear magnetic resonance (H1-NMR) spectra were conducted in Micro-Analytical unit at Cairo University on Bruker 400 MHz, proton magnetic resonance spectra were measured in hexadeutero dimethylsulfoxid (DMSO-d_6).

Nuclear magnetic resonance (^{13}C-NMR) spectra were obtained on Bruker 100 MHz with internal reference TMS δ=0, were measured by DEPT spectroscopy. Infrared spectra were recorded on a Fourier transformer infrared FT-IR spectrophotometer on Perkin Elmer model spectrum100. All melting points (mps) were determined by Gallenkamp melting point apparatus and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using glass and aluminum plates with Kieselgel G or Kieselgel GF 254 (Merck). The plates were run on the following systems:

- chloroform – methanol (different ratios).
- chloroform – ethanol (different ratios).
- ethyl acetate.

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

(33.0 g, 0.5 mole) malononitrile in 85ml ethanol was reacted with 4.0 g of 85% hydrazine hydrateand the mixture was heated to boiling, then added 12.0 g of 85% hydrazine hydrate at such a rate that the reaction mixture continued to boil without external heating. The mixture cooled to 0˚C, filtered and recrystallized using glacial acetic acid to yield the color-less needles of compound (1)(Fig. 1).



(1)

Fig.1. 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile

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

16.5 g (0.25 mol) malononitrile was added to a cooled solution of 7g (0.125 mol) of potassium hydroxide in 50 ml ethanol, was added 16.5 g (0.25 mol) of malononitrile. After 5-10 minutes under stirring and refluxing temperature the potassium salt of malononitrile dimer was precipitated. After 30 minutes of refluxing the mixture is cooled, then collected by filtration and washed with cold ethanol. The separated salt is dissolving in a small amount of water and acidifying with concentrated hydrochloric acid to pH4, filtered off and recrystallized from water to yielded colorless needles (Fig. 2).

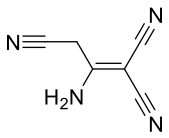


Fig. 2. malononitrile dimer (MND)

2.4 Synthesis of pyrazole azo dyes.

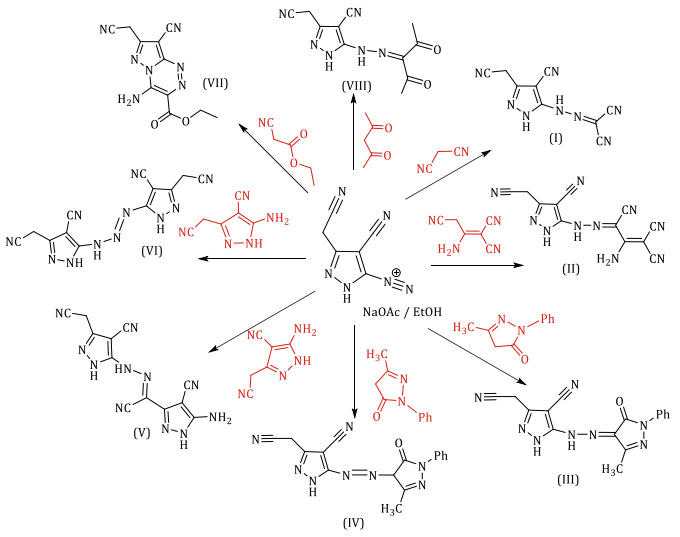
General procedure:

The mixtures of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile (1) (0.01mole) in concentrated HCl (x ml) was cooled to (0-5˚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°C) solution of active methylene compounds (0.01 mole) in an anhydrous sodium acetate (z mole) 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. Table 1 below shows the amounts of acid and base were added.

Table 1

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



Scheme 1

3. Results and 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 identical azo dyes, dependent on the medium of reaction, sometimes there are several possibilities for the precipitation of products, depends on the pH value, 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 (Scheme 1).

3.1 Synthesis of pyrazole

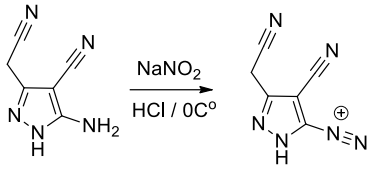
Preparation of pyrazole was carried out using Taylor (Taylor, E. 1959) procedure, proved melting point, IR which showed characteristic bands of amino group and nitrile groups also NMR spectrum showed signals of the amino groups which were identified by D_2O-exchange technique, the presence of desielded 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)(Fig. 1).

3.2 Synthesis of malononitrile dimer (2) (Fig. 2)

The synthesis of malononitrile dimer was carried out using Mittelbach (Mittelbach, M. 1985) methods. Melting point 169-172°C, 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 H^1 NMR (300MHz, DMSO-d_6) spectrum confirm that structure is 2-aminoprop-1-ene-1,1,3-tricarbonitrile: δ: 3.82 (2H, s, CH_2); 8.9 & 9.0 (2H, s, exchangeable, NH_2).

3.3 Diazotization of pyrazole

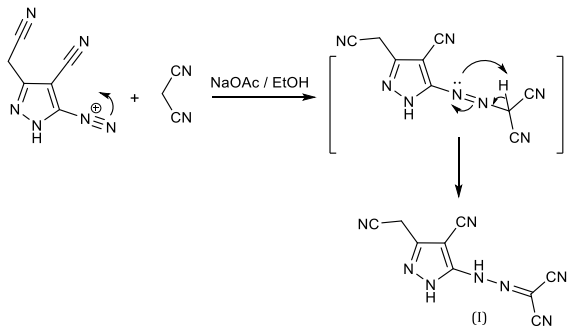
The first step the formation of diazonium salts of pyrazole, through treatment of pyrazole with nitrous acid (HNO_2) prepared from sodium nitrite ($NaNO_2$) and hydrochloric acid (HCl) at 0°C, diazotization reaction that proceeds (Scheme 2).



Scheme 2. Diazotization of pyrazole

3.4 Synthesis of pyrazole azo dyes

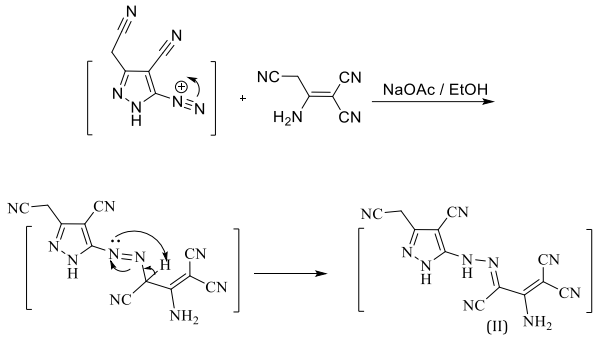
The clear diazonium salt solution was malononitrile molecule in sodium acetate. The dyes were characterized by elemental analysis and spectral methods. In addition, the effect of the pH value on the products yield of the dyes was reported. We noted that the pH value is very effective in the pyrazole dyes synthesis. 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. Moreover, carbon magnetic resonance spectrum showed signals at 112.21 and 112.66 ppm indicating appeared conjugate cyano groups in addition to other cyano groups of pyrazole. Malononitrile molecule is a a very active nucleophile reacted with a diazonium salt of pyrazole in good yield and quick coupling reaction, gives the expecting product (I)(Scheme 3) at a weak acidic was the best condition.



Scheme 3

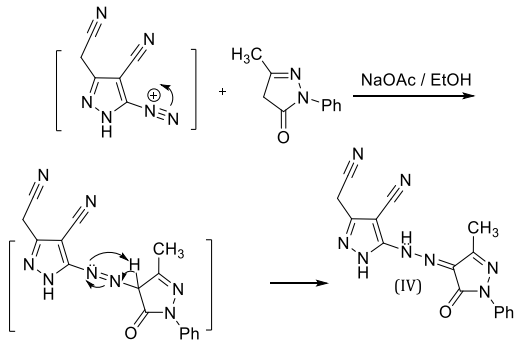
According to literature (El-Shafei, A. 2009), the basic ethanol in solution of MND was very active toward the coupling with the preformed pyrazolyl diazonium chloride in quick coupling reaction. The nucleophilic addition of methylene of MND is very active to react affording compound (II)(Scheme 4), despite the attempts changing the pH value each time gives the same expecting 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 infrared 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 C=N double bond of the compound. H^1-NMR spectra showed appearance of the methylene group on pyrazole at 3.75 ppm that also confirmed by spectroscopic technique where exhibit only one CH_2 at 17.63 ppm in absence of CH_2 of dimer sign to formation of C=N double bond that was apparent in ^{13}C-NMR at 111.72 ppm.



Scheme 4

Reaction of pyrazole with 3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one depends on the alteration of the pH value 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 methylene group on the pyrazolone on the diazonium salt enable in attacking chance of NH and disappearing of methylene group on pyrazolone and formation of (III), according to the suggested mechanism shown in scheme 6.

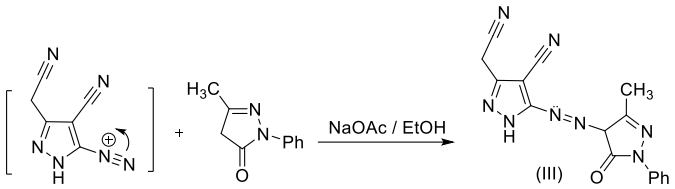


Scheme 5

NMR information was 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 is coincide at 4.23 ppm, which was proved by the D_2O exchange. In ^{13}C-NMR showed signals CH_3 and CH_2 at 12.18 & 15.87 ppm, while methylene group on 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 the active methylene group on the pyrazolone on the diazonium salt of pyrazole in pH less than 1 increase in attacking chance of the methylene and presence of NN double bond in the spectra leading to the actual product (IV) (Scheme 5) which is identified by comparison with the product (III) by M.P, TLC and next by NMR spectroscopic analysis technique that gave characteristic mode of the obtained product according to mechanism in the following reaction.

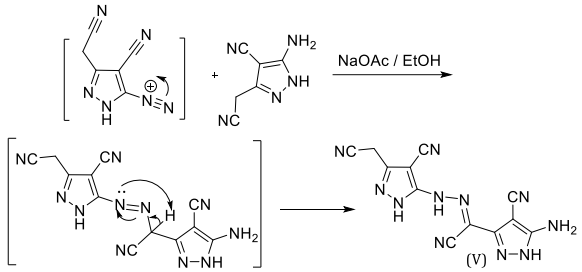
H^1-NMR spectra showed protons of the active methylene group as one singlet peak at 3.92 ppm. While the amino group is free appeared as signal at 6.43 ppm, as a reference to nucleophilic attack on the active methylene group on pyrazole and formation of CN double bond and this is confirmed by^{13}C-NMR 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 1 the reaction can be explained through nucleophilic attack of nitrogen of pyrazole ring on diazonium salt where the actual product was (VI)(Scheme 8), which is identified by M.P TLC and next by NMR spectroscopic analysis, the mechanism illustrated in the following mechanism:



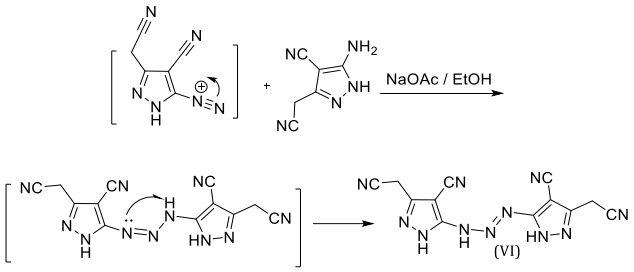
Scheme 6

Compound (IV) showed additional singlet signal in H^1-NMR spectra represent the second proton of methylene group on 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 on 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 increased addition of sodium acetate to the diazonium salt produced compound (V) (Scheme 7), suggested mechanism can be explained as following:



Scheme 7



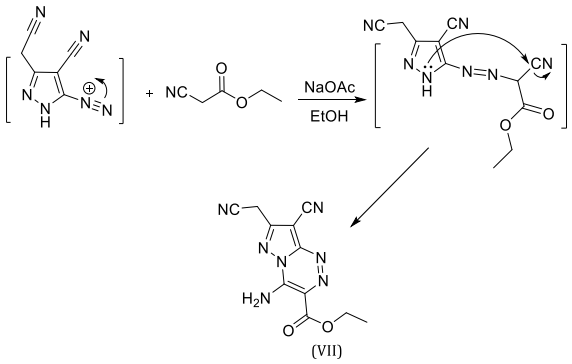
Scheme 8

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 (Fati Karc, F. 2008; Elnagdi, H. 2009) 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) (Scheme 9), proposed via nucleophilic attack of NH of the pyrazole on the conjugated cyano group, attempts of coupling reaction of pyrazole with ethyl cyanoacetate to synthesis an identical hydrazone were unsuccessful although modification were applied, were formed the suggested structure (VII).

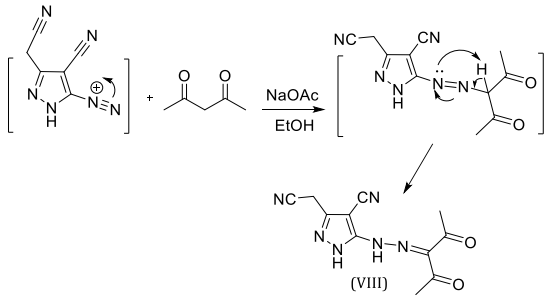
All the compounds obtained showed mostly the similar reaction features in creation of CN or NN double bond. In this reaction, the formation of product can be explained through nucleophilic attack of nitrogen of pyrazole ring on the conjugated cyano group followed by cyclisation of the product, which 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,



Scheme 9

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 on carbonyl group, that appear as clear signal in ^{13}C-NMR at 61.48 compared with methylene on pyrazole where showed a singlet at 16.93 ppm. DEPT spectroscopy analysis showed three varieties of protons CH_3 and different two CH_2. IR spectrum showed strong absorption band of conjugated CN of pyrazole ring appear at 2228cm^{-1}. While pyrazolyldiazonium chloride have been coupled with the active methylene on acetylacetone and afforded the corresponding hydrazone (VIII) (Scheme 10), 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 pH value of 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).



Scheme 10

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 on pyrazole ring which showed a single 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.

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