Faculty of Science
Chemistry Department

Synthesis and evaluation of Pyrazole and Pyrazolone derivatives as corrosion inhibitors for copper in alkaline medium and their biological activity.

A Thesis submitted for the Degree of Master of Science as a partial fulfillment for requirements of the Master of Science

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To
Department of Chemistry-Faculty of Science
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2016

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Acknowledgment

First, I would like to express my great thanks to God, for helping me to overcome all problems, which faced me throughout the work.

The auther wishes to express his deep thanks and sincere gratitude to ***Prof. Dr. Galal Hosni Sayed*** *Professor of Organic Chemistry, Faculty of Science, Ain Shams University, for his excellent supervision, helping, guidance and encouragement during the progress of the work.*

Also, I give all my thanks, regards and deep indebtedness to ***Prof. Dr. Nabel Abdel Moneem Negm*** *Professor of Applied Chemistry, Petrochemicals Department, Egyptian Petroleum Research Institute and* ***Dr. Mohammad Emad*** *Professor of Organic Chemistry, Faculty of Science, Ain Shams University for kind helping, encouragement, continuous advice and valuable discussions.*

Also, I want to express my deep thanks, my heartful respect and appreciation to my family to whom I am really in debt and especially to my parents for their patience.

Last, I would like to express my utmost thank for all my tutors and colleagues in Department of Chemistry, Faculty of Science , Ain shams University and all who gave me help and support for fulfillment of this work.

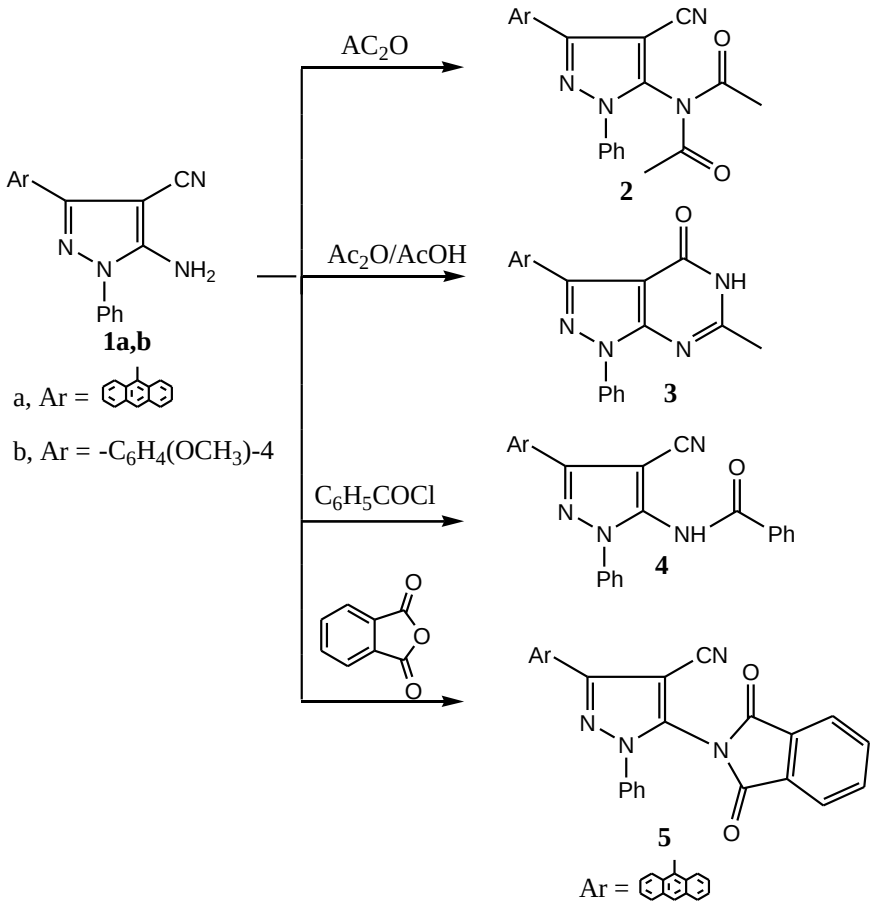
Kurls Ekram Anwer

Summary

The chemistry of pyrazoles has gained increasing attention due to its diverse pharmacological properties such as antiviral, antagonist, antimicrobial, anticancer, anti-inflammatory, analgesic, anti-prostate cancer, herbicidal, acaricidal and insecticidal activities.

The starting material enaminonitriles (1a,b) were prepared according to a previously reported method.

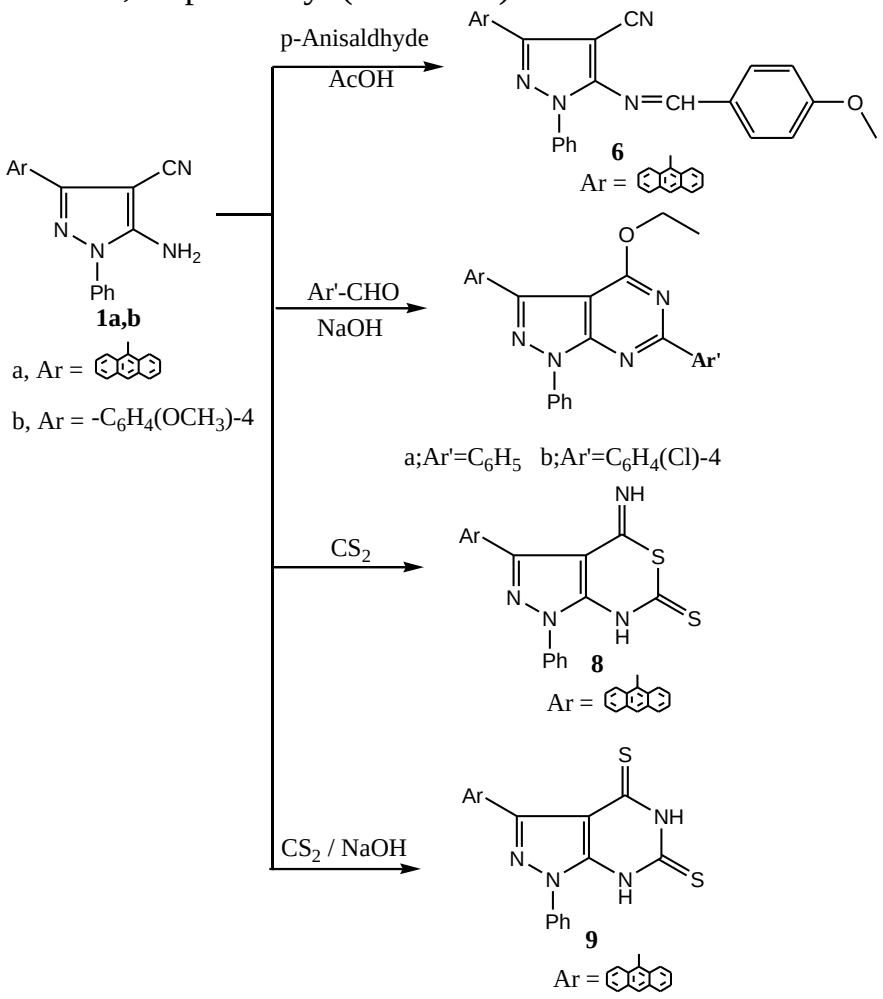
Treatment of (1a) with acetic anhydride, Ac_2O/AcOH mixture, benzoyl chloride and/or phthalic anhydride afforded N,N-diacetyl pyrazole (2), pyrazolopyrimidine (3), N-benzoyl pyrazole (4) and 1,3-dioxoisoindolinyl pyrazole (5) derivatives respectively. (Scheme 1)



Scheme 1

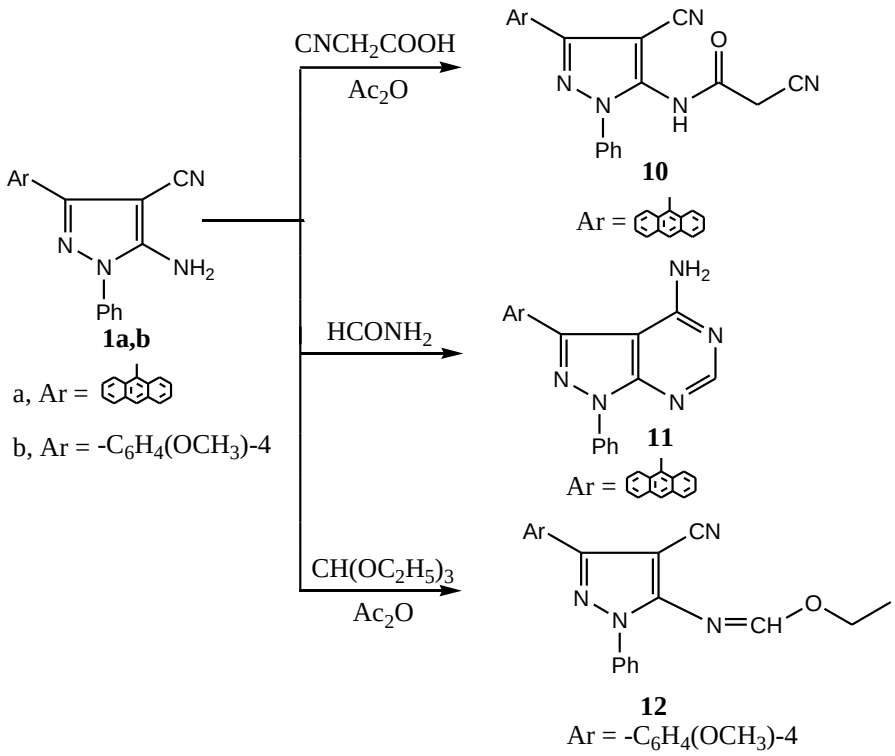
Enaminonitrile (1a) reacted with anisaldehyde in the presence of catalytic amount of acetic acid afforded Schiff base (6), while reaction of (1a), (1b) with benzaldehyde in the presence of NaOH, carbon disulfide and/or carbon disulfide in presence of NaOH afforded the corresponding

pyrazolopyrimidine (7a), (7b), pyrazolothiazine (8) and pyrazolopyrimidine (9) derivatives, respectively. (Scheme 2)



Scheme 2

When compound (1a) was allowed to react with cyanoacetic acid and/or formamide, cyanoacetamide (10) and pyrazolopyrimidine (11) derivatives were formed respectively, while reaction of 1b with triethyl orthoformate afforded compound (12). (Scheme 3)

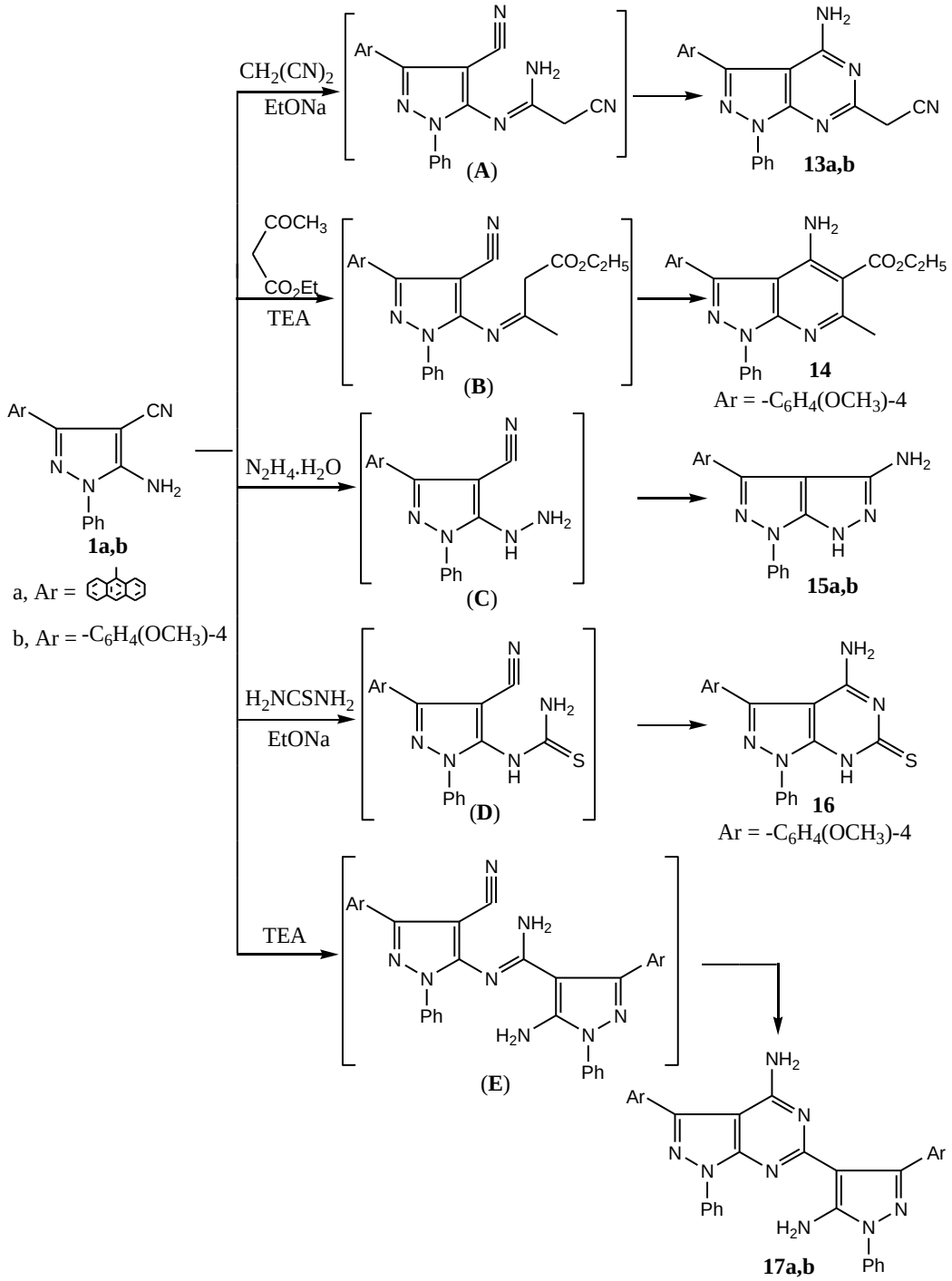


Scheme 3

The study was extended to explore the reactivity of the enaminonitriles (1a, b) towards some carbon and nitrogen nucleophiles.

Thus, reaction of (1a,b) with malononitrile and/or ethyl acetoacetate in the presence of a base afforded the acetonitrile and aminoester derivatives (13a,b) and (14), respectively. While treatment of (1a, b) with hydrazine hydrate and/or thiourea in the presence of sodium ethoxide afforded the pyrazolopyrazole (15a,b) and pyrazolopyrimidine (16), respectively.

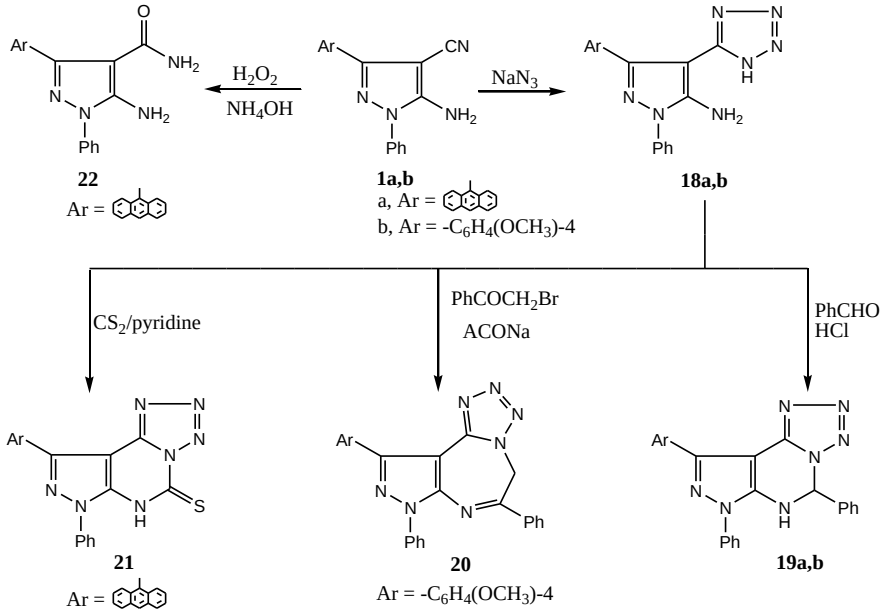
On the other hand boiling (1a,b) with triethylamine compound (17a,b), were obtained, respectively. (Scheme 4)



Scheme 4

Reaction of (1a,b) with sodium azide in the presence of ammonium chloride in dimethylformamide gave the tetrazole derivatives (18a, b), respectively. Reaction of compounds (18a, b) with benzaldehyde, phenacyl bromide/sodium acetate and/or carbon disulfide/pyridine afforded the tetrazolopyrimidine, tetrazolodiazepine and tetrazolopyrimidine thione derivatives (19a,b), (20) and (21), respectively. On the other hand stirring of

compound 1a with a mixture of hydrogen peroxide and ammonia solution afforded the amide derivative (22). (Scheme 5)



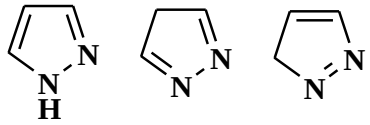
Scheme 5

The newly synthesized compounds were characterized by IR, ^{1}H-NMR and Mass spectral data and also tested against gram positive and gram negative, fungi and two human tumor cell lines.

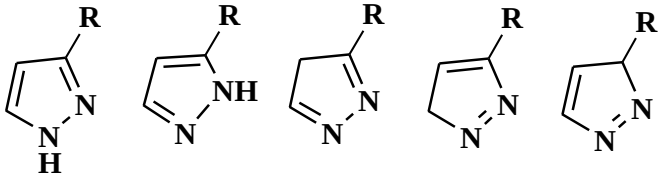
Chemistry of Pyrazoles

Pyrazole is a five membered and two nitrogen containing heterocyclic rings. Pyrazoles are rarely found in nature probably due to difficulty in the formation of N-N bond by living organisms.

Three tautomeric forms can be written for unsubstituted pyrazole (**1, 2, 3**) and five (**4, 5, 6, 7, 8**) for compounds in which the two carbon atoms adjacent to nitrogens carry different substituents.



1 **2** **3**



4 **5** **6** **7** **8**

Existence of forms 4 and 5 has been proved, but evidence for the isopyrazole form (**2, 6**) and for the pyrazolenine form (**3, 7, and 8**) is lacking. They are apparently capable of existence only for these derivatives carrying substituents in place of all four hydrogen atoms of the nucleus. Such compounds often show a tendency to rearrange to yield two pyrazoles. This indicates that the isopyrazoles and the pyrazolenines are less stable than the pyrazoles. [1]

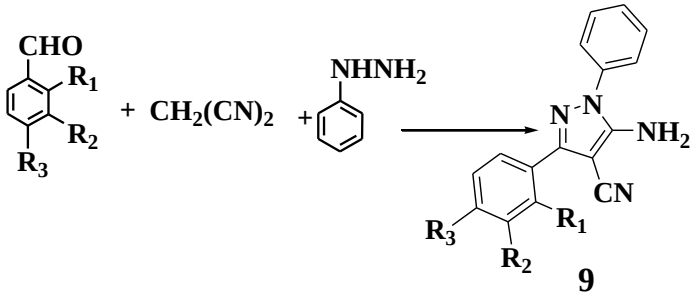
Synthesis of 5-amino-4-cyano-1H-pyrazoles

1. One pot multi component reactions (McRs)

The conventional multi-step synthesis of molecules involves more than one step, including the purification of compounds after each individual step, which leads to two main disadvantages: synthetic inefficiency and the production of large quantities of waste.

Signification attention has been paid to one-pot multi-component reactions (McRs) because of the high synthetic efficiency of these protocols.

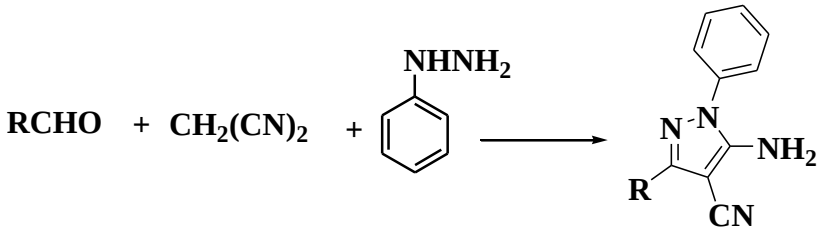
So, 5-amino-1H-pyrazole-4-carbonitrile derivatives (**9**) can be prepared from easily available and simple starting materials: aldeyde, malononitrile and phenylhydrazine, in one pot multicomponent reaction. [2]



9

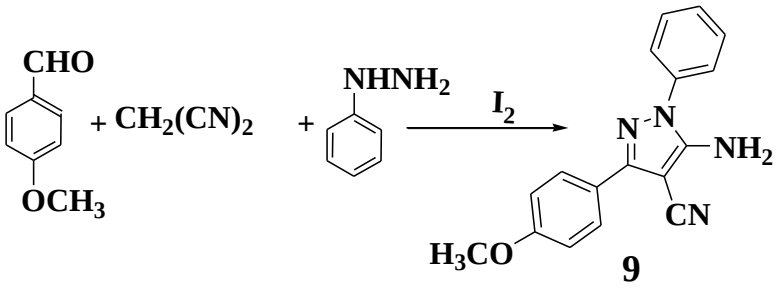
R_1 =H,OCH_3 R_2 =H,NO_2 R_3 =H,OCH_3 , Cl, F, $N(CH3)_3$,NO_2 ,CH_3

Similarly, a series of new pyrazole derivatives (**10**) have been synthesized by simple grinding of aromatic aldehydes, malononitrile and phenylhydrazine.[3]



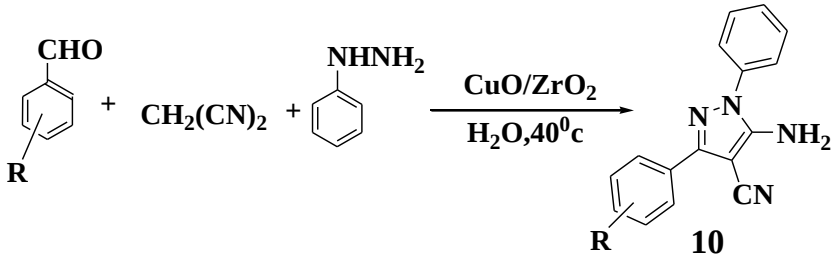
10

Madhulika, S.etal synthesized 5-amino-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (**9**) via reaction of p-anisaldehyde, malononitrile and phenylhydrazine in presence of iodine. [4]



9

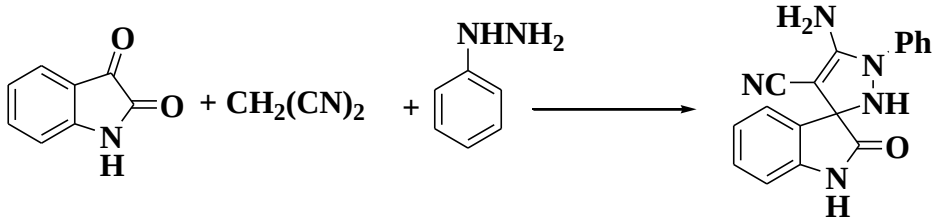
However, Suresh, M.et al synthesized a series of 5-amino-3-(aryl)-1-phenyl-1H-pyrazole-4-carbonitrile(**10**) through the reaction of phenylhydrazine , malononitrile, and aromatic aldehydes in presence of CuO/ZrO_2 as catalyst at room temperature.[5]



10

R= 4-Br-Ph ; 4-CF_3-Ph ; 2-Cl-Ph

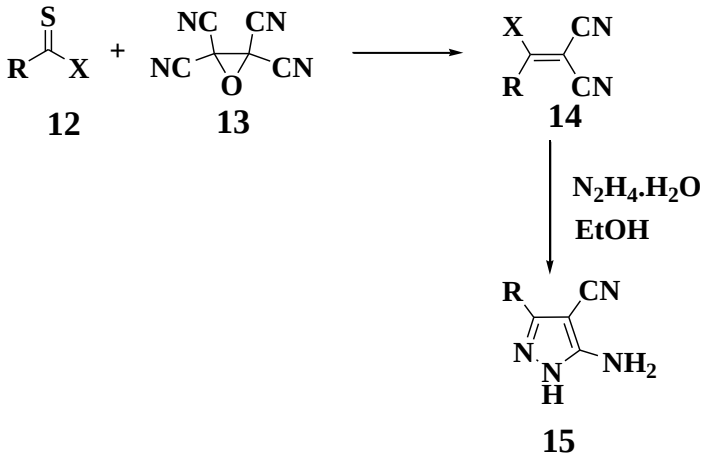
Reaction of isatin, malononitrile and phenylhydrazine gave 5'-amino-2-oxo-1'-phenyl-1',2'-dihydrospiro[indoline-3,3'-pyrazole]-4-carbonitrile(**11**). [2]



11

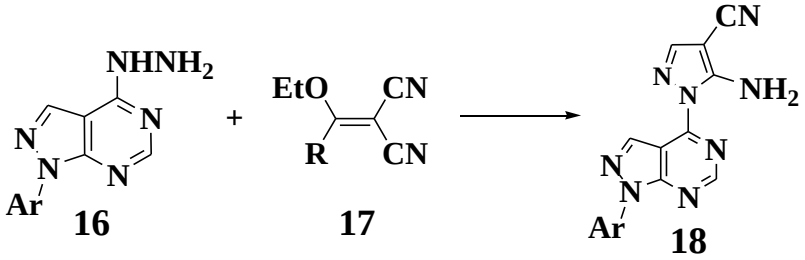
2. From thioamide

Reaction of thioamide (**12**) with tetracyanoethylene oxide (**13**) at room temperature in benzene with stirring gave the corresponding dicyanoethylene compound (**14**), which on reaction with hydrazine hydrate gave the corresponding 3-substituted-5-amino-4-cyanopyrazole derivative (**15**). [6]



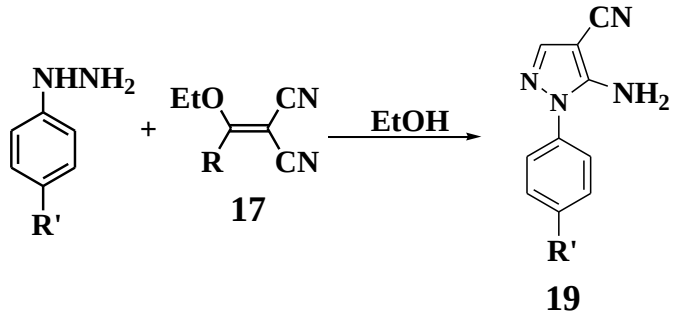
3. ***From ethoxymethylene malononitrile***

Reaction of 1-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl hydrazine (**16**) with ethoxymethylene malononitrile (**17**) in ethanol afforded 5-amino-1-(1-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1H-pyrazole-4-carbonitrile (**18**). [7]



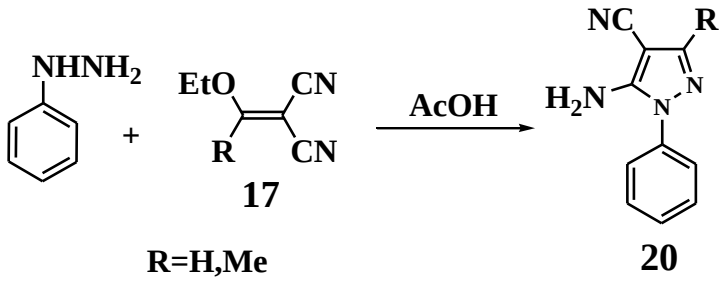
R=H

Reaction of p-substituted phenylhydrazine hydrochloride and ethoxymethylene malononitrile (**17**) in ethanol gave 5-amino-1-aryl-1H-pyrazole-4-carbonitrile derivative (**19**). [8, 9]

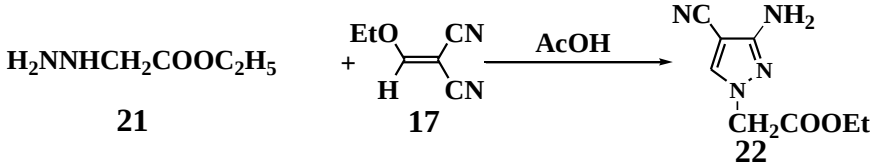


2a: R'=H 2b: R'=Cl 2c: R'=CH_3 R=H

Similarly, 5-amino-4-cyano-N'-phenyl pyrazole (20) was prepared through the reaction of ethoxymethylene malononitrile (17) with phenylhydrazine in acetic acid. [10]

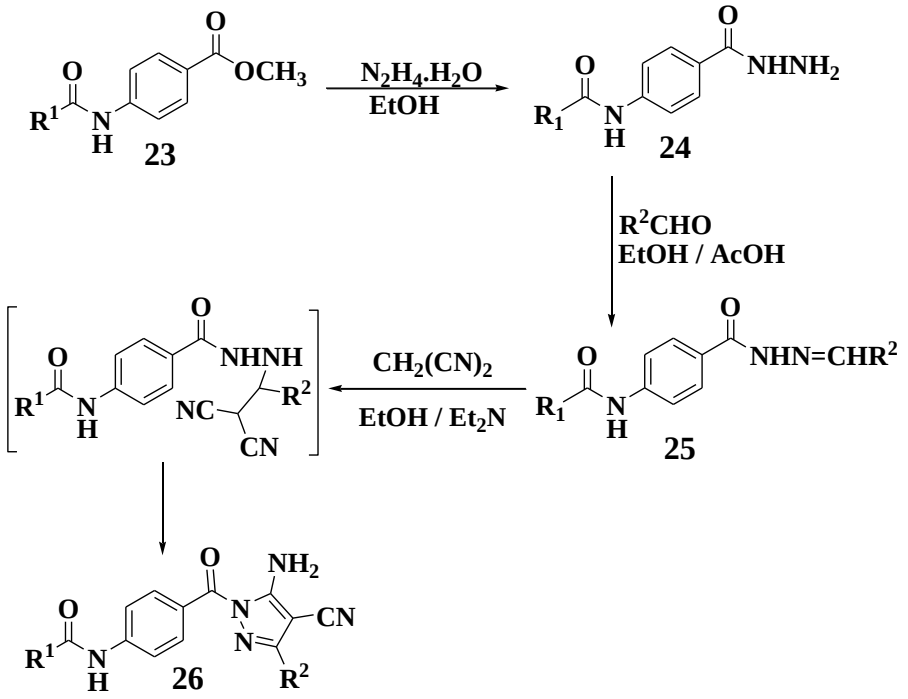


However, reaction of ethoxymethylene malononitrile (**17**) with ethyl hydrazino acetate (**21**) gave the 5-amino-4-carbonitrile derivative (**22**). [11]



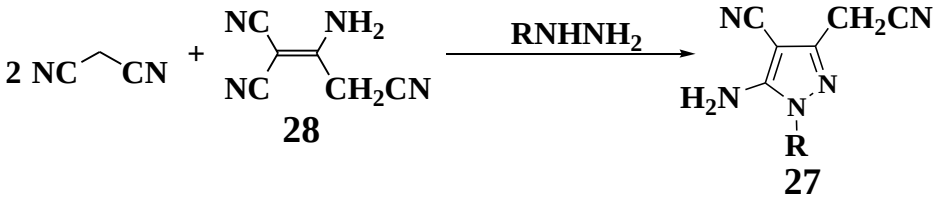
4. <u>From hydrazide</u>

Treatment of 2-benzoylamino-N-carbonylmethylbenzoate (**23**) with hydrazine hydrate in boiling ethanol gave 2-benzoylamino-N-carbonylbenzoyl hydrazide (**24**). Reaction of compound (**24**) with aldehyde or aldose gave substituted aroyl hydrazone derivative (**25**) which on reaction with malononitrile in ethanol gave the corresponding 5-amino-4-cyano-3-arylpyrazole derivatives (**26**). [12]



5. ***From malonodinitrile dimer***

1-Substituted-5-amino-4-cyano-pyrazole-3-acetonitriles (**27**) are formed by the reaction of malonodinitrile dimer (**28**) with hydrazines. [13]



Reactions of 5-amino-4-cyano-1H-pyrazoles

1. With aliphatic acid and acetic anhydride

Condensation of the amino-cyano compound (**15**) with formic acid gave the hydroxypyrazolo-pyrimidines (**29**), which can be converted to the chloropyrazolo-pyrimidines (**30**) by chlorination with thionyl chloride. [14]