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A SHORT REVIEW ON SYNTHESIS OF PYRAZOLE DERIVATIVES & THEIR PROPERTIES

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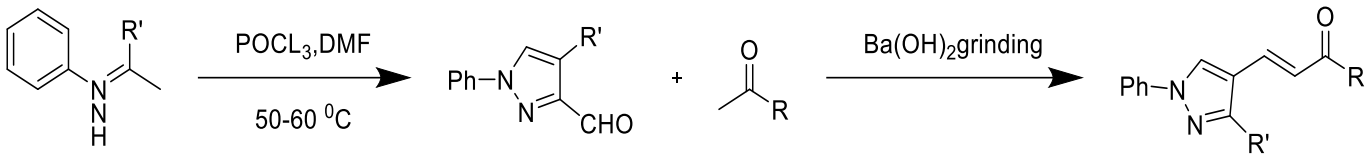
Abstract: To evaluate properties of pyrazole & derivatives Antibiotic resistance has improved as a result of a number of factors, causing scientists to look for novel drugs to treat multidrug resistant bacteria. In this frame, Pyrazole based compounds have a wide range of pharmacological activity, and their derivatives have a high level of functional variability, making them more suitable in the development of new therapeutic drugs. Due to developing antibiotic resistance, antibiotic efficacy is being challenged all over the world.

Key words :- pyrazole, synthesis, antibiotic, derivatives, reflux,

Introduction:-The pyrazole &pyrazolone component can be involved in a wide variety of medicinally essential compounds. In synthetic and pharmacological chemistry, pyrazolones are a prominent class of chemical compounds. These compounds have a wide range of biological properties, such as edaravone, which can be used to treat brain and cardiac ischemia. Many research investigations have been conducted on pyrazolone derivatives due to their possible biological functions. These include anti-tumor, anti-tubercular, anti-inflammatory, anti-fungal, anti-bacterial, anti-bacterial, anti-malarial, and anti-depressant qualities.[1]Pyrazolone derivatives are a key component of a wide range of active pharmaceutical ingredients, agro-chemicals, and dyestuffs, along with chelating and extracting agents. Chemists and biologists have focused considerable attention on the research of pyrazolone derivatives in recent years due to the growing application of their synthesis and bioactivity. But the major problem still remains in devising a cost-effective, environmentally friendly, and time-efficient path to construct such techniques. Several advanced techniques for synthesizing pyrazolone of natural compounds have been developed in recent years, but generating a moiety with medical and commercial value on a large scale remains a difficulty. According to available literature searches, methyl and phenyl-substituted pyrazolone compounds have massive pharmacological characteristics. The pyrazolone ring is a structural motif that appears in a number of pharmaceutically active drugs. The pyrazolone skeleton is essential in physiologically active compounds because of its ease of manufacture and high biological activity. Due to its demonstrated value as synthetic intermediates for the manufacture of numerous bioactive molecules of coordination complexes as well as in the style of functional materials, pyrazolones have gained a lot of interest in organic and medicinal chemistry. Pyrazolones are also oxidation resistant. A dehydrogenate inhibitor is known as pyrazolone.[2]

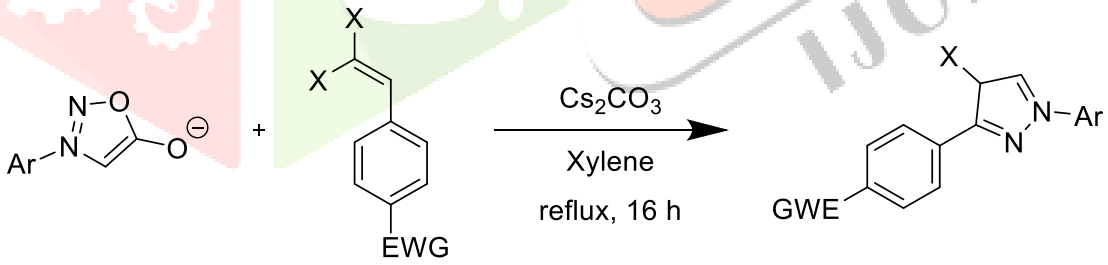
Scheme 1



R' = Ph, 4-CH3C6H4, 4-CH3OC6H4, 4-FC6H4, 4-BRC6H4, 4-CLC6H4, 4-NO2C6H4, 4-C2H5
R = 2-OH-C6H4, 2-furyl, 2-thienyl, 4-CL-C6H4, 4-BRC6H4, 4-FC6H4, 4-CH3C6H4, 4-C2H5-C6H4, 4-CH3OC6H4, Ph, CH3.

Chalcones are typically produced through the Claisen Schmidt condensation of ketones and aryl aldehydes catalyzed by alkali metal hydroxide. Several different catalysts, including heterogeneous catalysts, zncl$_2$, P_2O_5-piperidine, Lewis's acid, and Mg-Al-O^{t}Bu hydrotalcite, have also been documented for use. In addition, the condensing reactions were observed to use strong alkali under phase transfer catalyzed circumstances, barium hydroxide in ethanol, and microwave situations. However, all of the disclosed procedures make use of organic solvents during condensation operations and product isolation by extracting. Because of their volatile nature, these organic solvents have been deemed the most harmful to human health and the environment. In order to be eco-friendly, the creation of procedures under solvent-free situations has also increased in importance. In this paper, we will describe a simple but fast method for producing pyrazole chalcones by grinding a mixture of pyrazole aldehydes, acetophenones, and activated barium hydroxide in a mortar and pestle for 5 to 10 minutes in the absence of any solvent. The product can also be made simply by acidifying the solution before separating it. Thus, we hoped that synthesis of these chalcones using C-200 would be superior to previously reported methods because (i) it would take less time, (ii) it would be solvent-free, (iii) it would yield higher yields, (iv) there would be no side reactions like the Cannizaro reaction, (v) the workup would be very simple, and (vi) there would be no need for any organic solvent for chalcone extraction. In conclusion, we have described a generic and effective method for synthesizing pyrazole-substituted chalcones with C-200 as a base. Condensation is clean with this base in a high yield in a short period of time, as well as using green chemistry, i.e., solvent-less synthesis. The uniqueness of this approach is that no organic solvent is necessary, either as a reaction medium or as a solvent for extracting (scheme 1).

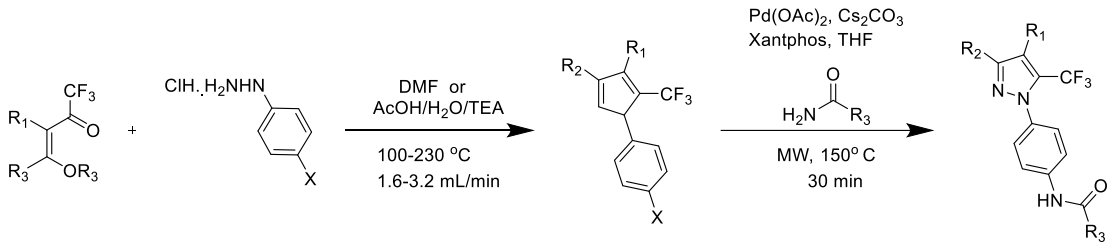
Scheme 2



EWG= NO_2 , CN & X = Cl , Br

1,3-Diaryl-4-halo-1H-pyrazoles were discovered to be key intermediates that may be quickly transformed into 1,2,4-triaryl- or 1,2,5-triaryl-substituted pyrazoles via a C–C coupling reaction catalysed by Pd. Yang Y & Kuang C established a simple and effective method for producing a series of 1,3-diaryl-4-halo-1H-pyrazoles in moderate to high yield via 1,3-dipolar cycloaddition of 3-arylsydnones and 2-aryl-1,1-dihalo-1-alkenes.[4] The previous research reports on the simple and effective formation of a series of innovative 1,3-diaryl-4-halo-1H-pyrazoles in moderate to outstanding yields. The approach utilised involves the 1,3-dipolar addition reactions of 3-arylsydnones and 2-aryl-1,1-dihalo-1-alkenes. A Pd-catalyzed C–C linking reaction was used to turn 1,3-dialyl-4-halo-1H-pyrazoles into 1,2,4-triaryl-or 1,2,5-triaryl-substituted pyrazoles.[5] (scheme 2).

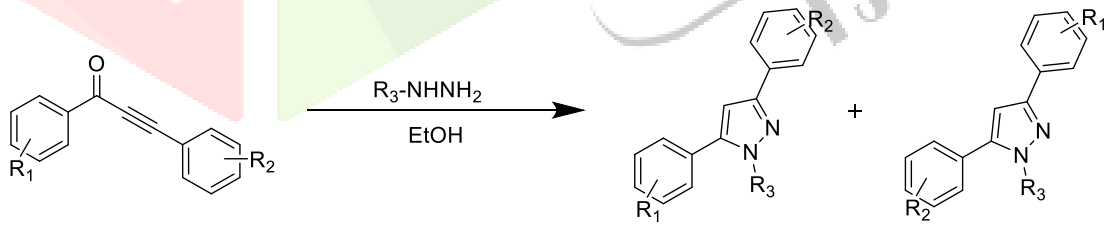
Scheme 3



R1= CO_2Et, H R2= H, CF_3 R3= Et , H

Pyruvate kinase (PK) is a glycolysis mediator and a rate-limiting enzyme that acts as a catalyst in the final stage of glycolysis. PKM2 is seen in huge proliferating cells such as cancer and embryonic cells, and is one of four PK isoforms (PKL, PKR, PKM1, PKM2) generated by two genes (pkrl and pkm). PKM2 has the potential to change cancer cell metabolism. In this sense, tiny molecule PKM2 activators may impact cancer metabolism by stabilizing the tetrameric form. As a consequence, the activators may offer a unique anticancer therapy approach.[6]Obermayer used microwaves to create a series of 4-(pyrazol-1-yl) carboxanilides that inhibit canonical transient receptor potential channels.[7] As a result, Obermayer decided to investigate the potential of the Pd-catalyzed variant of the amide N-arylation reaction. He achieved a promising conversion of approximately 87.5% when he used our previously improved[8] microwave conditions on the current substrates [5 mol% $Pd(OAc)_2$ as precatalyst, Xantphos as ligand, and Cs2CO3/THF as base/solvent combinations at 150 C and a 20 min reaction rate]. A promising microwave methodology was established by simply adjusting this method by increasing the reaction period to 30 minutes while leaving the remaining reaction parameters the same. Further attempts to refine the process by changing the base, ligand, or solvent were ineffective, yielding only partial conversion of the 1-(4-halophenyl)-1H-pyrazoles. After flash chromatography, these aryl halides were efficiently synthesized into the corresponding carboxanilides in a 56–92% yield. In recent times, Buchwald-Hartwig reactions[9] have been shown. The reactor coils were sonicated throughout the approach to avoid solid bridging and constriction from interrupting the flow regime. An approach to converting our optimised microwave parameters into a continuous flow protocol flopped due to limitations in the available flow equipment as well as nonuniformity of the reaction mixture when applying the improved reaction conditions. Finally, the two newly improved phases (continuous flow cyclocondensation and microwave batch Buchwald-Hartwig amidation) were integrated into a single approach, which used the product stream obtained in the first flow cyclocondensation step directly.[10](scheme 3)

Scheme 4



R_1 or R_2 = H, NO_2 , Cl , OMe , F

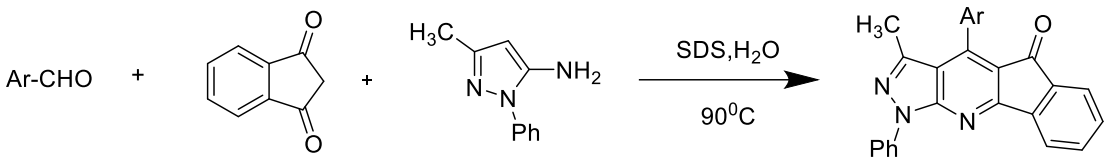
R_1 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, ME

Synthesis of 3,5-diarylpyrazoles from acetylenic ketones and hydrazine derivatives, as shown in Scheme 4.

A regioselective synthesis of an unsymmetrical 1,3,5 substituted pyrazole derivative was required as part of a therapeutic candidate development programme. In the perspective of the synthesis of 3,5 diarylpyrazoles, Bishop was interested in the elements that influence the regioselectivity of this type of response. They first investigated the cyclocondensation of acetylene ketones on methyl hydrazine or aryl hydrazine in ethanol, which produces two regioisomeric pyrazoles.[11] that are hard to distinguish. They made a variety of acetylenic ketones and studied how they interacted with methyl hydrazine and (substituted) phenyl hydrazines. These compounds were made by carbonylating phenyl acetylenes with aryl iodides with Pd catalysts or coupling aryl acid chlorides with phenyl acetylenes with copper catalysts. The variation in regioselectivity reported while utilizing methylhydrazine (ratio 27/28 = 93:3 to 97:3) rather than an arylic hydrazine (ratio 28/27 = 87:13 to 99:1) is due to the reality that the nitrogen trying to carry a methyl group

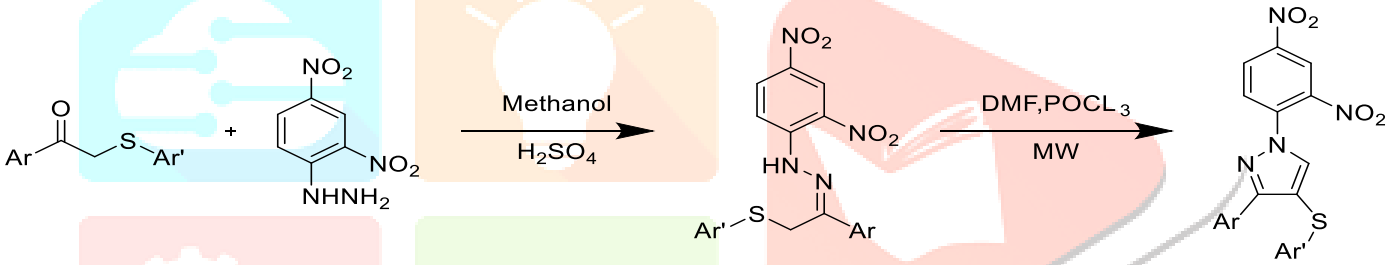
is far more nucleophilic and it will respond by Michael addition to the triple bond of acetylenic ketone guided by the intramolecular configuration of an imine. When an aryl group is swapped by a hydrazine, the primary amine is the most nucleophilic and will target the triple bond first, followed by the secondary amine targeting the carbonyl.[12](scheme 4)

Scheme 5



To limit the amount of hazardous materials and byproducts developed by industrial processes, improved focus has been focused on using less harmful and also more ecologically friendly materials in the development of new synthetic technologies. An efficient three-component synthesis using an aromatic aldehyde, 3-methyl-1-phenyl-5-aminopyrazole, and 1,3-indenedione was developed for the synthesis of indeno [2',1':5,6] pyrido[2,3-d] pyrazole derivatives in the presence of sodium dodecyl sulfate, an anionic surfactant, and water as the reaction medium.[13] This technique uses a procedure that is both ecologically friendly and straightforward to implement.[14](scheme 5)

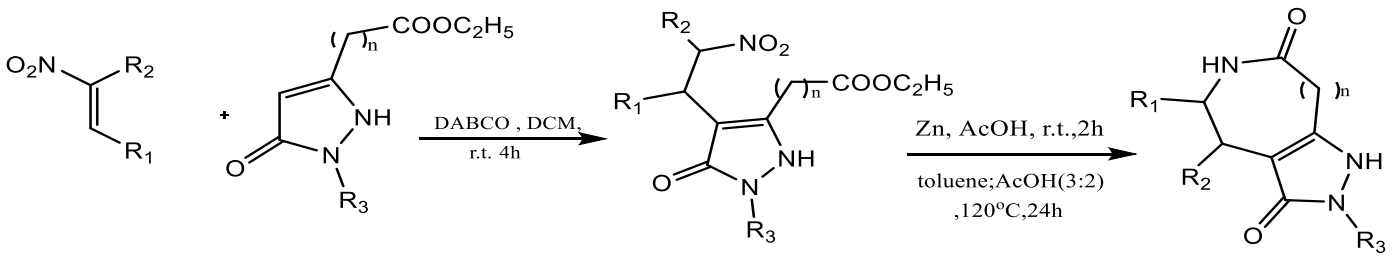
Scheme 6



Ar = C6H5, p-CH3C6H4, p-OCH3C6H4, p-ClC6H4,
Ar' = C6H5, p-ClC6H4, p-CH3C6H4

Hydrazones were treated with a lot of dimethylformamide and phosphorous oxychloride before being micro waved for 30-60 seconds to get a lot of 1-(2.4-dinitrophenyl)-3-aryl-4-(arylsulfanyl)-1H-pyrazoles.[15] Hydrazones were produced by coupling 2,4-dinitrophenylhydrazine and substituted phenacyl aryl sulphides. It is generally known that hydrazones containing α-methylene hydrogen's undergo formylation, followed by ring closure and the formation of a pyrazole ring via the Vilsmeier reaction.[16] The identified hydrazone precursors are substituted phenacyl aryl sulphides. These sulphides were created by mixing a 1:1:2 mixture of substituted phenacyl bromide, substituted thio-phenol, and triethyl amine in ethanol for 2 hours while stirring. The sulphides have already been reported, and they have now been prepared using a slightly modified method. The sulphides were treated in methanol with 2,4-dinitro phenylhydrazine to give quantifiable yields of 2,4-dinitro phenylhydrazones. Under microwave irradiation, the dinitrophenylhydrazones were exposed to the Vilsmeier reaction. The compound was irradiated with microwaves for 30 to 60 seconds after being treated with excess dimethylformamide and phosphorous oxychloride. TLC was used to monitor the reaction's progress, and after it was finished, the liquid was placed onto ice and extracted with chloroform. Recrystallisation was used to purify the final products. The pyrazoles were produced in high yield.[17] (scheme 6)

Scheme: 7

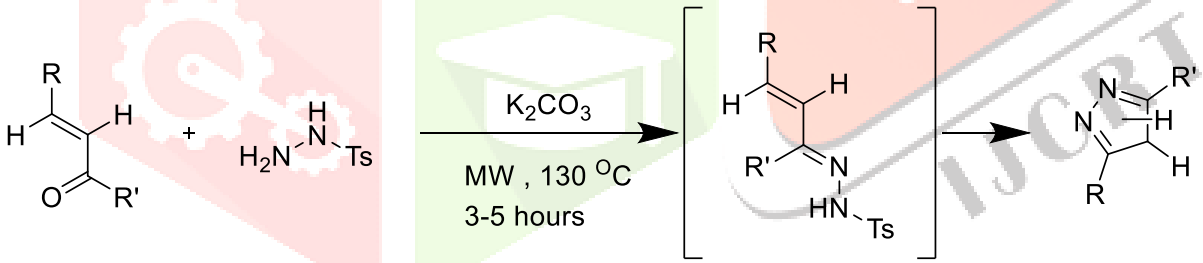


R_1 = phenyl, R_2 = H, R_3 =phenyl, n = 0

Parekh, synthesized heterocyclic fused pyrazolone from nitroolefins and 3- ethoxy carbonyl (methylene) pyrazoline-5-one via DABCO catalysed Michael addition and Reductive ring –closing strategy with a yield of 74-92% [18]. We get also a pyrazolo [3,4-c]-pyridine-3,7-dione and pyrazolo[3,4-d]-azepine-3,7-dione [18].

Pyrazoline-5-ones can exist in different tautomeric form [19]. This Michael adduct might then undergo reductive cyclization to provide a new class of heterocycles with a pyridine ring fused to pyrazolone. We described how we employed a Michael addition reductive cyclization route to develop and synthesize pyridone fused pyrazolones[18]. DABCO catalyst mediated the reaction in excellent yield in 4 hours. First step, deprotonated of pyrazolone by the base leads to carbanion A which then undergoes an intermediate, after abstracting a proton from the protonated base, intermediate created the required Michael adduct through a C-N tautomeric shift. Reductive cyclization of Michael adducts under the catalyst of Zn, AcOH at room temperature, at 2 hours and toluene, AcOH at 120˚C,24 hours we get a pyrazolo[3,4-c]-pyridine -3,7-diones.Heterocycles containing pyrazolone rings belong to class of molecules that studied because of their application in drug molecules,[20] they are attractive target in the field of medicinal chemistry and drug discovery.[21] (scheme 7)

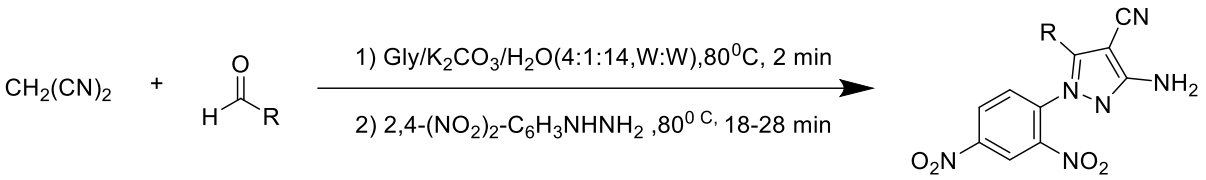
Scheme 8



R= -Ph, R'= -PH, $-CH_3$.

The development of a new eco-friendly synthetic pathway to the synthesis of pyrazole derivatives. Anna Corradi et al. Recently published a new solvent –free microwave-based process for the production of pyrazoles from tosyl hydrazones of α-unsaturated carbonyls with a beta hydrogen in the presence of K_2CO_3 and p-toluene sulfonyl hydrazide. Microwave irradiation was used to activate the cells in the cells in this method (MWI). The suggested microwave based solvent free technique yielded good results in terms of yields and reaction speed, indicating that this process is an environmentally friendly, quick, and simple way to make pyrazoles from, α-unsaturated ketones with β-hydrogen.[22] This last strategy must be deemed the optical synthetic route taking into consideration atom economy, step reduction, and additional methanol elimination in the synthesis of tosylhydrazones in full accordance with green chemistry principles on the basis of equal yield and very similar reaction duration.[22] (scheme 8)

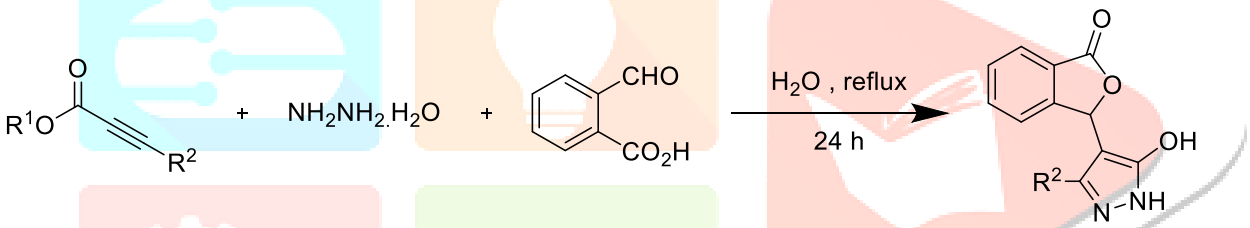
Scheme 9



R= 4-$O_2NC_6H_4$

Beyzaei et al synthesized Green one-pot of Novel Polysubstituted pyrazole derivatives as potential antimicrobial agent. An efficient, environmentally friendly, cost-effective, and quick procedure was used to make 5-amino-1-H-pyrazole-4-carbonitriles. Malononitrile, mono or disubstituted benzaldehydes and 2,4-dinitrophenylhydrazine were combined in a one pot two step procedure to create polyfunctional pyrazoles 4a-f in height yields with glycerol/K_2CO_3 as the reaction media and catalyst, the best results were obtained [23]. we used glycerol as a green, cheap, non-toxic, inflammable and readily available solvent was present in reaction. This reaction not obtain at room temperature. So improved ability of solvent with increasing temperature to 80˚C. Formation of Schiff bases as major product in glycerol showed that presence of K_2CO_3 catalyst is required for the synthesis of pyrazoles.[23] This pyrazole the antibacterial properties against Proteus mirabilis. (scheme 9)

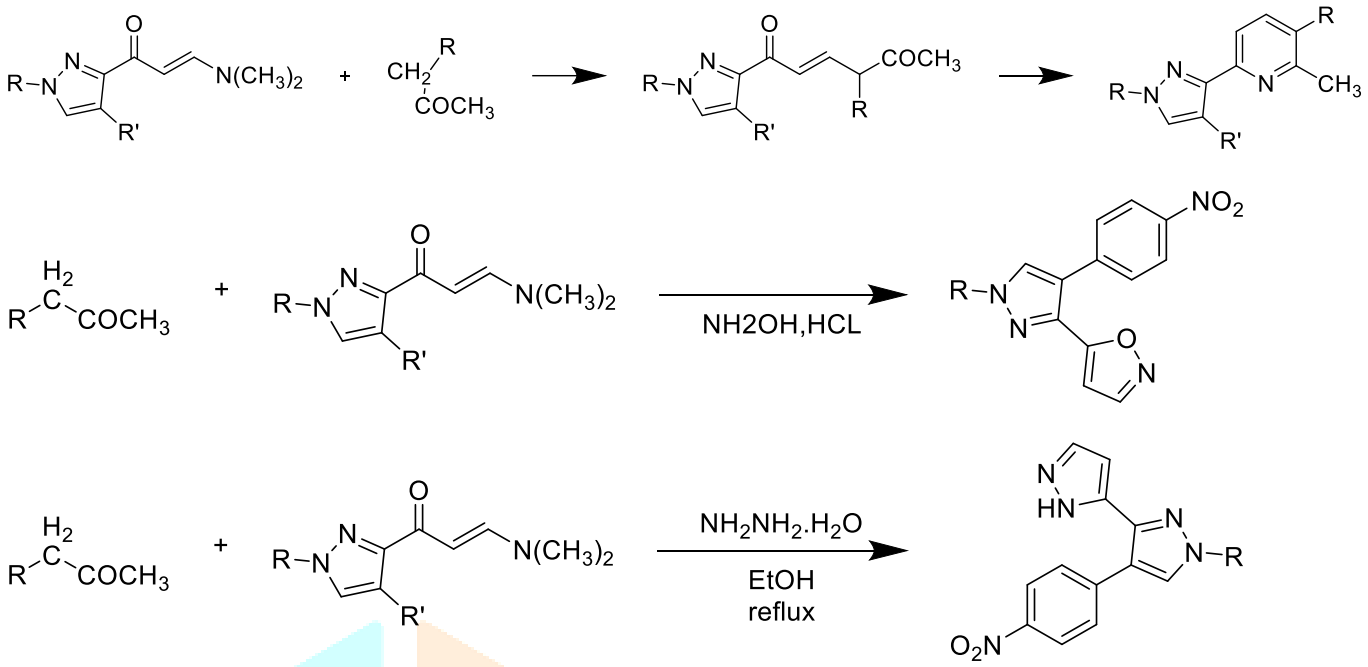
Scheme 10



R^1= Me , Et , R^2= Ph.

A pyrazol-3-one intermediate develop in situation from acetylenic esters and hydrazine hydrate could be trapped by 2-formylbenzoic acid to give a phthalide-fused pyrazole product. Reacted under the water, reflux condition which formed an intermediate.[24] the sequential addition of reactant successfully gave the phthalide-fused pyrazole derivatives in good isolated yields. Different solvents such as H_2O, EtOH, CH_3CN, toluene, and THF were result showed that, and when the reaction proceeded with good yield when water was utilized as solvent.[25] Bazgir and co-workers at 100˚C for one day is disclosed. this eco-friendly reaction required only filtration and washing with ethanol. This method shows characteristics, for instance, application of H_2O as a solvent, uncomplicated workup of product, and reduced waste formation without employing any catalyst. (scheme 10)

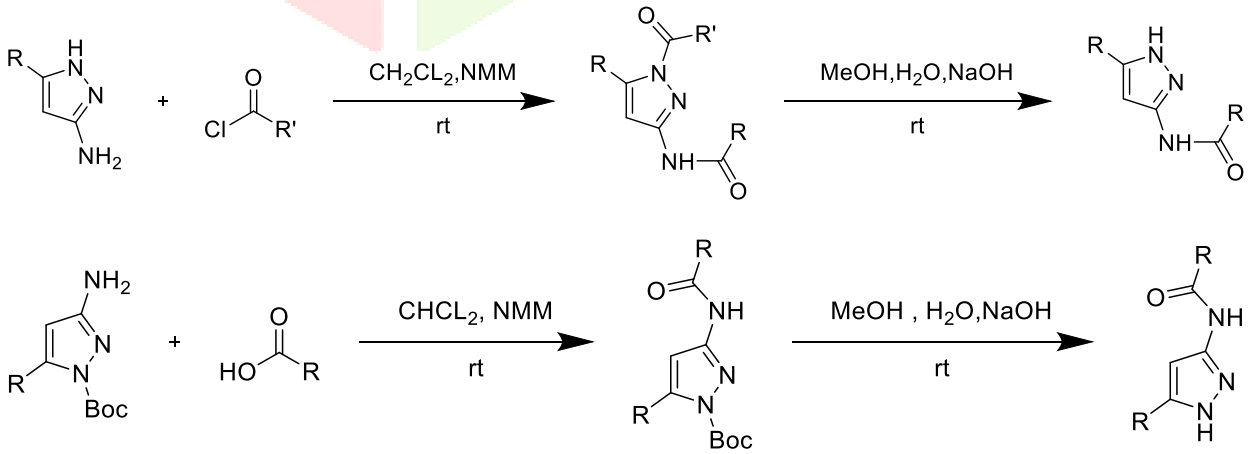
SCHEME 11



R=$COCH_3$, R'=C_6H_5
R=$COCH_3$, R'=4-$CH_3C_6H_4$
R=COOEt , R'=C_6H_5
R=COOEt , R'=4-$CH_3C_6H_4$

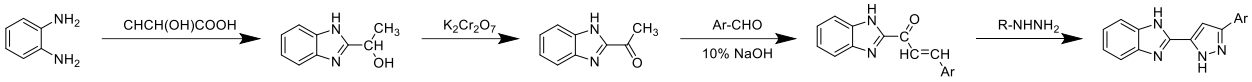
Using previously published chemicals, Al-mater et al.[26] disclosed the synthesis of pyrazolic enaminones. 3-[E-3-(N, N-dimethylamino) acryloyl] 3-[E-3-(N, N-dimethylamino)acryloyl] 3-[E-3-(N,N-dimethyl -4-(4-nitrophenyl) -1-aryl-1H-pyrazoles are a kind of pyrazole that has one aryl and one hydrogen attached to it.[27]Enaminones react with C-nucleophiles such 2,4-pentanedione, ethyl 3-oxobutanoate, and N-nucleophiles like hydrazine hydrate and hydroxylamine hydrochloride to generate 6-(pyrazol-3-yl)-pyridine derivatives and isomers, 1H 1'H-3,3'-bipyrazoles, and pyrazolylisoxazoles.[28](scheme 11)

SCHEME 12



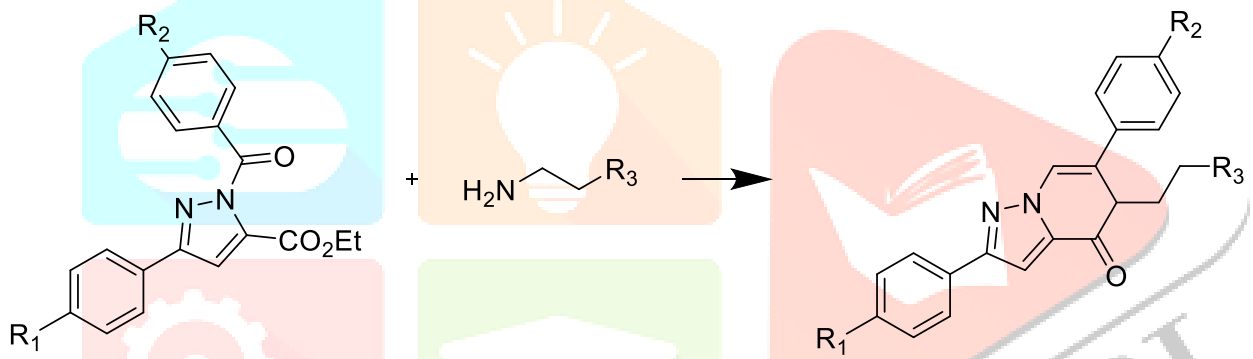
Pevarello synthesized 3-aminopyrazole derivatives via two distinct protocols:[29] first, pairing a proper 5-substituted 3-aminopyrazole with an acid chloride, guided by preferential basic deacetylation of the endocyclic acetyl residue to yield the final compounds. And EDCl (1-ethyl-3- (3-diethylaminopropyl) carbodiimide) was used as a condensing agent to combine 1-Boc protected 5-substituted 3-aminopyrazole with a carboxylic acid. The resultant inter- mediate was then deprotected to produce final chemicals.[30](scheme 12)

SCHEME 13



Kalirajan et al. used microwave irradiation to create 1-(1H-benzo[d]imidazol-2-yl) ethanol by reacting o-phenylenediamine with lactic acid. When permitted to react with various aldehydes under basic circumstances, oxylation of the hydroxyl group yields keto derivative, which yields chalcone derivatives. Under microwave circumstances, the compound was synthesized by a cyclization process with hydrazine in ethanolic sodium acetate.[30] (scheme 13)

SCHEME 14



R_1 = HCl, OMe
R_2 = H HCl Cl OMe
R_3 = OCH_2CH_2OH, $N(CH_2CH_2)_2O$

He began by condensing in the presence of xylene to yield target compound, but the yield was low, so many attempts with different solvents and condition were made. Finally, this reaction was carried out in a solvent -free environment while being microwave irradiated, and the product was discovered to be in good yield.[28]

Conclution:- Pyrazole derivatives and their complexes with various metals have been synthesized for a long time. The bioactivity of pyrazole derivatives was mostly investigated in depth. Recent efforts have been made to better understand the characteristics of pyrazole derivatives. There are also some difficulties to overcome. These difficulties include increasing synthesis efficiency for higher yields, developing new pyrazole derivatives with bioactivity in the sub-micro molar range, and precisely assessing the derivatives' characteristics.

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