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Pyrazoles: Synthetic Strategies and Their Pharmaceutical Applications-An Overview

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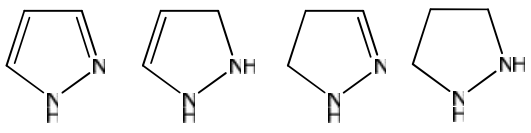
Abstract: Pyrazoles are an important class of five membered heterocyclic compounds; are widely found as the core structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities. Pyrazoles have been the recent target of numerous methodologies, mostly due to their prevalence as scaffolds in synthesis of bioactive compounds and reactions in different media. The aim of this review is to provide an up to date developments in the synthetic strategies, biological activities associated with pyrazole derivatives. Different synthetic methodologies and the diverse pharmacological activities of pyrazole moiety was discussed.
Key Words: Pyrazoles, Microwave, Ultrasound, antimicrobial, anti-tubercular, anti-inflammatory, analgesic, anticonvulsant.

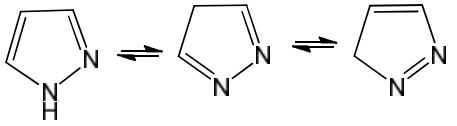
Introduction

Pyrazoles (**1a**) are the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Among the two nitrogen atoms; one is basic ane the other is neutral in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. The aromatic nature arises from the four π electrons and the unshared pair of electrons on the –NH nitrogen. The partially reduced forms of pyrazole are named as pyrazolines (**1b** or **1c**); while completely reduced form is pyrazolidine (**1d**).

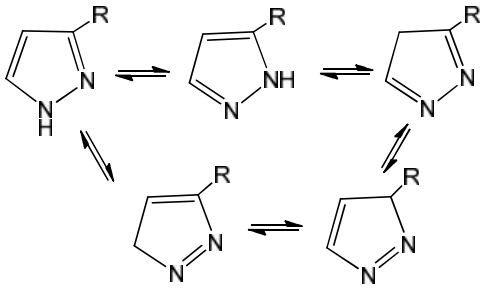


1a **1b** **1c** **1d**

Pyrazole is a tautomeric substance; the existence of tautomerism cannot be demonstrated in pyrazole itself, but it can be inferred by the consideration of pyrazole derivatives. Unsubstituted pyrazole can be represented in three tautomeric forms (Scheme-1). For the pyrazole derivatives in which two carbon atoms neighboring the nitrogen atoms on the ring have different substituents, five tautomeric structures are possible (Scheme-2).



Scheme-1

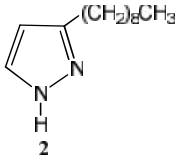


Scheme-2

Pyrazoles and its derivatives, a class of well known nitrogen heterocycles, occupy an prime position in medicinal and pesticide chemistry for their diverse biological activities. They have been known to exhibit antimicrobial, analgesic, anticancer, anti-tubercular, anti-inflammatory, antidepressant, anticonvulsant, antihyperglycemic, antipyretic, antihelmintic, antioxidant and herbicidal properties. The pyrazole ring is present as the core in a variety of leading drugs such as Celebrex, Sildenafil (Viagra), Ionazlac, Rimonabant and Difenamizole etc. Pyrazole analogues have found use as building blocks in organic synthesis for designing pharmaceutical and agrochemicals; and as bifunctional ligands for metal catalysis.

Pyrazoles have illustrious history; in 1883, a German chemist Ludwig Knorr was the first to discover antipyretic action of pyrazole derivative in man, he named the compound antipyrine. When he attempted to synthesize quinoline derivatives with antipyretic activity, accidentally obtained antipyrine (2,3- dimethyl-1-phenyl-3-pyrazolin-5-one) which has analgesic, antipyretic and antirheumatic activity; which stimulated interest in pyrazole chemistry.

The first natural pyrazole derivative was isolated by Japanese workers Kosuge and Okeda in the year 1954, till their discovery it was thought that pyrazoles could not be obtained naturally. They isolated 3-*n*-nonylpyrazole (**2**) from Houttuynia Cordata, a plant of the "*piperaceae*" family from tropical Asia; which showed antimicrobial activity. They also isolated *levo*-β-(1-pyrazolyl) alanine (**3**) an amino acid from watermelon seeds (Citrullus Vulgaris).



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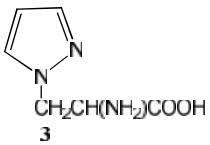

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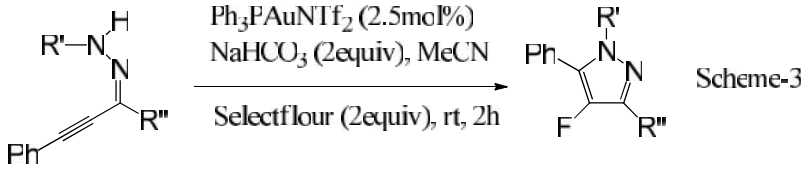
Synthesis Of Pyrazoles:

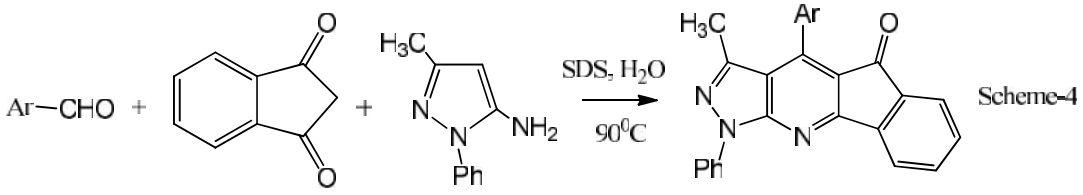
The wide range of biological activities associated with pyrazoles has made them popular synthetic targets. Numerous methods have been developed for preparation of substituted pyrazoles. In general, pyrazoles are synthesized by (*i*) the reaction of 1,3-diketones with hydrazines, (*ii*) 1,3-dipolar cycloaddition of diazo compounds with alkynes and (*iii*) the reaction of α,β-unsaturated aldehydes and ketones with hydrazines. In this review more emphasis was given for the synthetic strategies developed for the synthesis of pyrazole analogues in recent years and were critically discussed.

A mild and efficient protocol to access fluoropyrazoles for the first time based on ubiquitous alkyne moieties as backbones involving a gold-catalyzed tandem aminofluorination of alkynes in the presence of selectfluor (an electrophilic fluorine source) was developed by Qian et al (Scheme-3)[1]. The method has advantages of mild reaction conditions, high yields, broad substrate scope and a simple one-pot procedure.



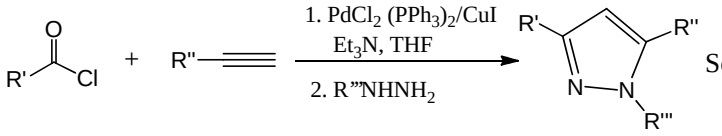
Scheme-3

An efficient three-component reaction of an aromatic aldehyde, 3-methyl-1-phenyl- 5-aminopyrazole and 1,3-indenedione was designed 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 using water as reaction medium (Scheme-4)[2]. This protocol has an environmentally benign procedure having simple operation.



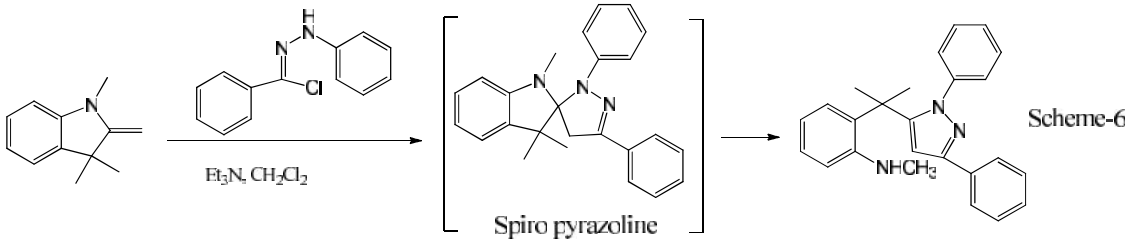
Scheme-4

Tandem reactions refer to two reactions operating in succession in the same reaction vessel. An efficient and general one-pot three-component procedure for the construction of pyrazoles via a tandem coupling-cyclocondensation sequence catalyzed by $Pd(PPh_3)2Cl_2$/CuI was reported (Scheme-5)[3]. Enones were synthesized from acid chlorides and terminal alkynes, and were converted *in situ* into pyrazoles by the cycloaddition of hydrazines. The method has easy isolation and simple workup procedures.



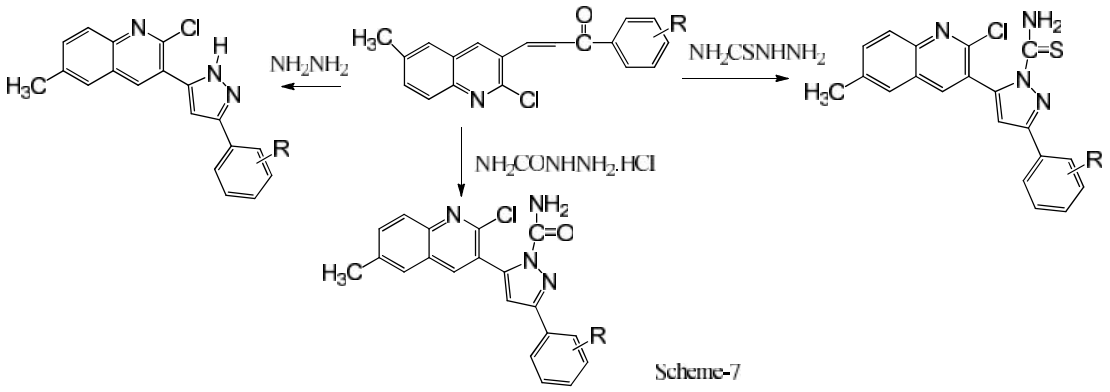
Scheme-5

The pyrazole compounds were constructed through the Huisgen cycloaddition of 2-methylene-1,3,3-trimethylindoline and an *in situ* generated nitrile imine. The newly formed spiro-pyrazoline intermediate presumably then undergoes a ring opening/elimination process to afford a novel 1,3,5-trisubstituted pyrazole derivative (Scheme-6)[4].



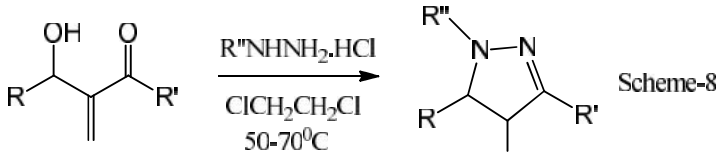
Scheme-6

Microwave irradiation is pollution free and eco-friendly route in organic synthesis. As microwave irradiation facilitates the polarization of the molecule, the reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. For instance; Mistry et al[5] reported the synthesis of various pyrazole derivatives both by conventional and microwave-assisted synthesis (Scheme-7). It was found that the reaction carried out in acetone using conventional method requires about 5-7hr, while microwave irradiation method requires only 4-7 min. The synthesised compounds have been tested of their antibacterial and antifungal activities.



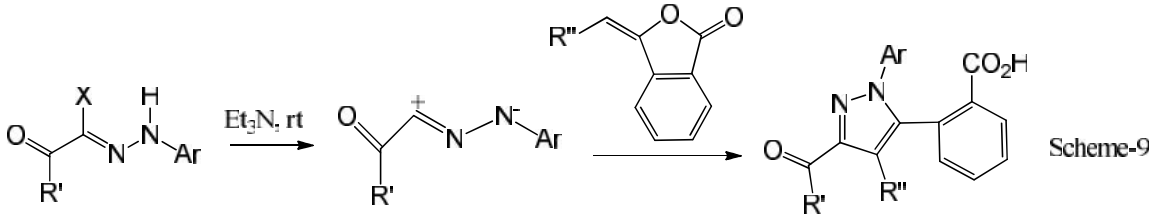
Scheme-7

The reaction of Baylis–Hillman adduct and phenyl hydrazine in dichloroethane at 50-70°C for about 6 hrs afforded the tetrasubstituted pyrazole derivatives with very high regioselectivity of products in 89% yield (Scheme-8)[6]. The reaction follows via the successive hydrazone formation, cyclisation and double bond isomerisation sequence under reflux conditions.



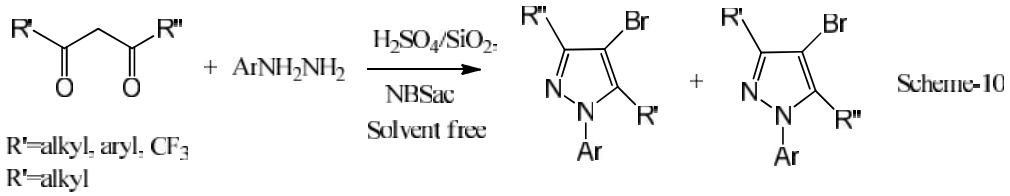
Scheme-8

The nitrile imines generated *in situ* from the hydrazonoyl halides react with 3-propylidenephthalide and 3-benzylidenephthalide in refluxing benzene to afford 1,3,4,5-tetrasubstituted pyrazoles (Scheme-9)[7]; which involves initial formation of the spiro intermediates via 1,3-dipolar cycloaddition of nitril imines, ultimately underwent ring opening via 1,3-hydrogen shift to aromatic pyrazole derivatives.



Scheme-9

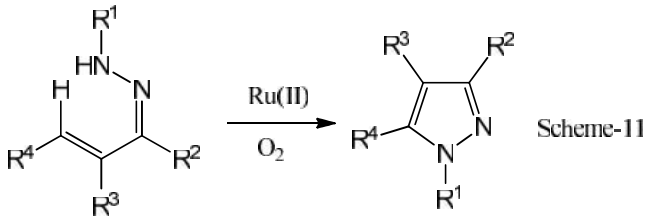
Alinezhad and co-workers[8] reported a facile one-pot regioselective preparation of 4-bromopyrazoles with high yields from 1,3-diketones, arylhdrazines and *N*-bromosaccharin (NBSac) in the presence of silica gel supported sulfuric acid (H_2SO_4/SiO_2) under solvent free conditions (Scheme-10). When *N*-bromosaccharin was added and mixed thoroughly, 3,5-dimethyl-4-bromo-*N*-phenylpyrazole was obtained in excellent yield within 7 min.



Scheme-10

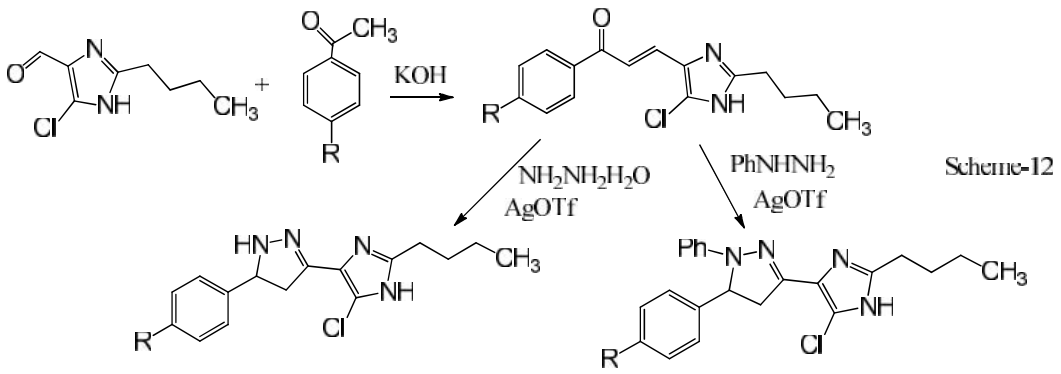
A novel Ru(II)-catalyzed oxidative C-N coupling method has been reported for the synthesis of highly diversified tri- and tetrasubstituted pyrazoles from easily accessible starting materials (Scheme-11). Dioxygen

gas is employed as the oxidant which plays an essential role in the catalytic cycle of C-H activation. This method is useful for making a variety of multisubstituted pyrazoles, most of which are difficult to access with conventional methods. The reaction demonstrates excellent reactivity, broad scope, high tolerance of functional groups and high yields[9].



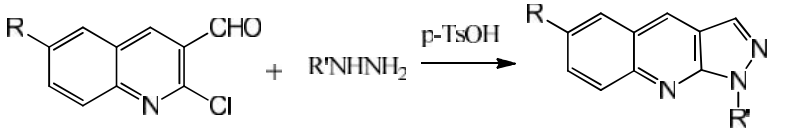
Scheme-11

Silver triflate Ag (I) used as Lewis acid catalyst in organic reactions for effective and novel transformations in organic synthesis. A series of imidazole-pyrazole derivatives were synthesized using silver triflate as catalyst from chalcones by Claisen-Schmidt condensation of appropriate acetophenones with imidazole aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. Silver activates the carbonyl carbon of the chalcone and add hydrazine hydrate or phenyl hydrazine followed by cyclo-reversion to provide products in good yields in short reaction time (Scheme-12)[10]. The synthesized compounds were tested for their antibacterial and antifungal activities.



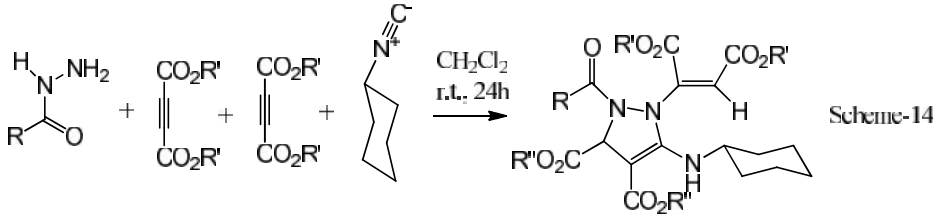
Scheme-12

The synthesis of pyrazolo[3,4-*b*]quinolines from β-chlorovinylaldehydes and phenylhydrazine using *p*-TsOH under microwave irradiation (Scheme-13)[11]. It was found that *p*-TsOH is most adaptable and simplest catalyst that causes noticeable rate enhancement in microwave irradiation synthesis.



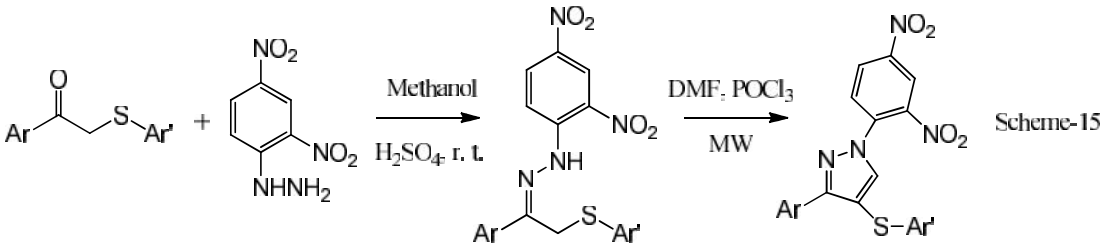
Scheme-13

The highly functionalized 1*H*-pyrazole derivatives were synthesised by a one-pot isocyanide-based cascade four-component reaction between arylcarbohydrazides, dialkyl acetylenedicarboxylates, and cyclohexyl isocyanide (Scheme-14)[12]. This approach has the potential in synthesis of various functionalized 1*H*-pyrazole derivatives due to the easy availability of the synthetic approach and the neutral ring closure conditions.



Scheme-14

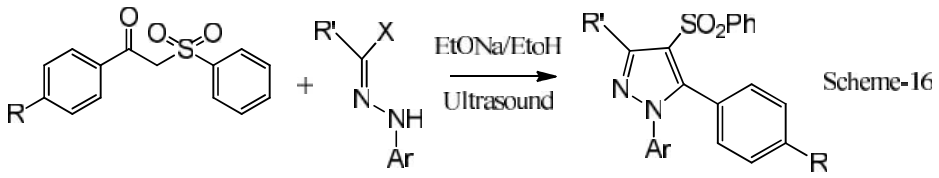
Hydrazones were treated with excess dimethylformamide and phosphorous oxychloride and irradiated under microwaves for 30-60 seconds to get 1-(2.4-dinitrophenyl)-3-aryl-4-(arylsulfanyl)-1*H*-pyrazoles in good yields (Scheme-15)[13]. Hydrazones were in turn prepared from 2,4-dinitrophenylhydrazine and substituted phenacyl aryl sulfides.



Scheme-15

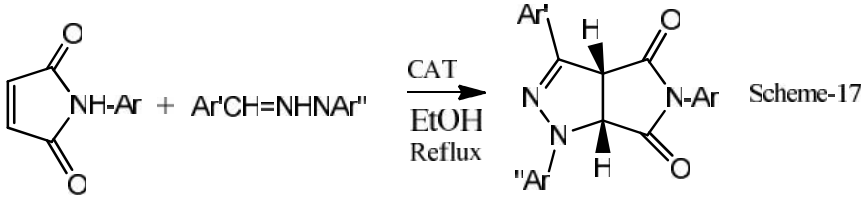
Mercaptoheterocyclic compounds on treatment with bromo ethylacetate in the presence of base afforded thioacetate derivatives which on subsequent treatment with hydrazine hydrate yielded acylated hydrazine derivatives. Reaction of these acylated hydrazine derivatives with ketene dithioacetal derivatives in methanol under reflux condition afforded sulphur bridged pyrazole derivatives. These synthesised pyrazole derivatives were tested for their antibacterial activity against both gram positive and gram negative bacteria[14].

In recent times, ultrasonic conditions in organic synthesis has gained prime place. Reactions carried out under silent and a condition reduces the time of reactions from several hours to minutes and improves the yields compared to that of conventional conditions. For example; Saleh et al[15] reported the synthesis of novel pyrazoles by the reaction of the carbanions of 1-aryl-2-(phenylsulphonyl)ethanone with different hydrazonyl halides (Scheme-16). It was observed that α-sulphonyl carbanion was found to be a good nucleophile for reaction with different hydrazonyl halides. The reaction evidences that ultrasound irradiations enable some reactions to occur which could not be carried out under silent condition.



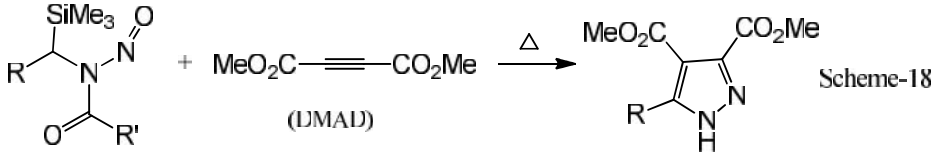
Scheme-16

Rai and co-workers[16] reported a new approach for the synthesis of pyrazoles via 1,3-DC of acetyl acetone and *in situ* generated nitrile imines. Their reaction afforded the regioselective cycloadducts in good yield. Very recently Kumar *et al* reported the synthesis of 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydropyrazoles by Huisgen cycloaddition of *in situ* generated nitrile imines and *N*-aryl maleimides, the cycloadducts obtained showed promising antibacterial, antifungal and antioxidant activities (Scheme-17)[17-18].



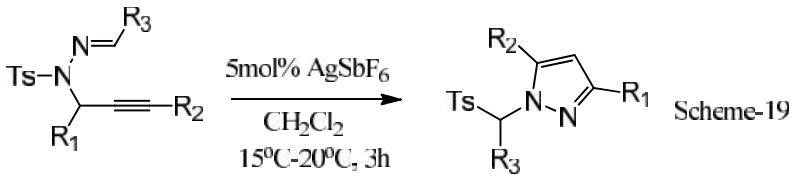
Scheme-17

A novel synthesis of pyrazole derivatives using polymer-supported α-silylnitrosoamide derivatives is reported by Washizuka et al[19]. Pyrazole derivatives were obtained by 1,3-dipolar cycloaddition of polymer-supported azomethine imines with dimethyl acetylenedicarboxylate (DMAD) in good yields (Scheme-18). The azomethine imines were generated from polymer-supported α-silylnitrosoamides by a 1,4-silatropic shift. Intramolecular 1,4-silatropic shift of the α-silylnitrosoamide gave the polymer-supported azomethine imine which underwent 1,3-dipolar cycloaddition with the dipolarophile. The products can be easily separated from the polymer without any cleavage operation.



Scheme-18

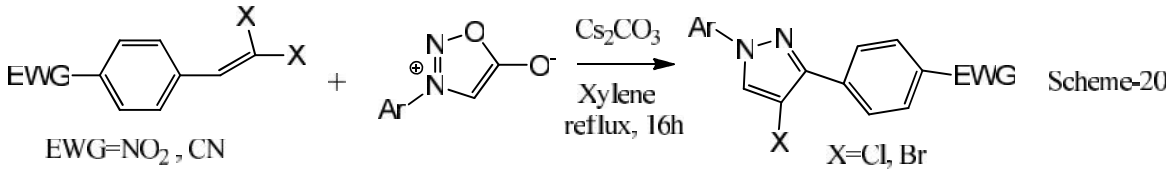
A simple, efficient and regioselective procedure for the silver(I)-catalyzed formation of 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles from propargyl *N*-sulfonylhydrazone is reported by Lee and co-workers[20] (Scheme-19). It was observed that during the reaction, a migration of sulfonyl groups (Ts, Ms) occur. The method was found practically useful and good functional group-compatibility under mild reaction conditions.



Scheme-19

R_1=H,Me; R_2=H,Me,Ph; R_3=Ph, Styrenyl, alkyl

1,3-Diaryl-4-halo-1*H*-pyrazoles were found to be important intermediates that can easily be converted into 1,2,4-triaryl- or 1,2,5-triaryl-substituted pyrazoles via a Pd-catalyzed C–C coupling reaction. For instance; Yang et al[21] reported a convenient and efficient synthesis of a series of 1,3-diaryl-4-halo-1*H*-pyrazoles in moderate to excellent yields by 1,3-dipolar cycloaddition of 3-arylsydnones and 2-aryl-1,1-dihalo-1-alkenes (Scheme-20).

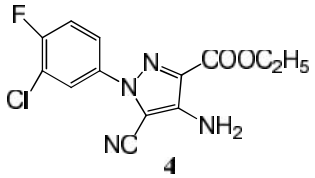


EWG=NO_2 , CN

X=Cl, Br

Scheme-20

Aldehyde phenyl hydrazones undergo oxidative dehydrogenation with chloramine-T to give nitrile imines, which are trapped *in situ* by ethyl oleate to afford 8-(5-aryl-4-octyl-2-phenyl-3,4-dihydro-2*H*-pyrazol-3-yl)-octanoic acid ethyl esters in good yield and have showed moderate antimicrobial and antioxidant activities[22-23]. Fluoro chloro aniline on diazotization forms diazonium salt which on reaction with ethyl cyanoacetate gives the intermediate. The intermediate when cyclized with chloroacetonitrile using triethylamine as the base a series of novel substituted pyrazoles (**4**); and were screened for their antibacterial and anti-oxidant activity[24].



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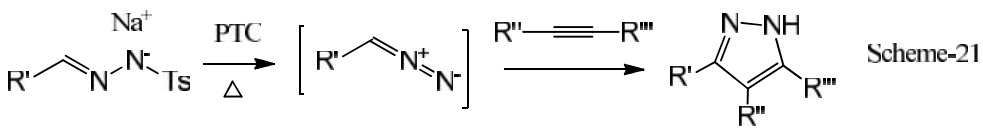
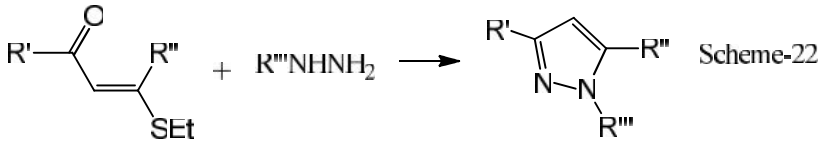
Aggarwal et al[25] reported a new user-friendly one-pot procedure for regioselective synthesis of 3,5-disubstituted pyrazoles by the 1,3-dipolar cycloaddition reactions of diazo compounds (Scheme-21).



Scheme-21

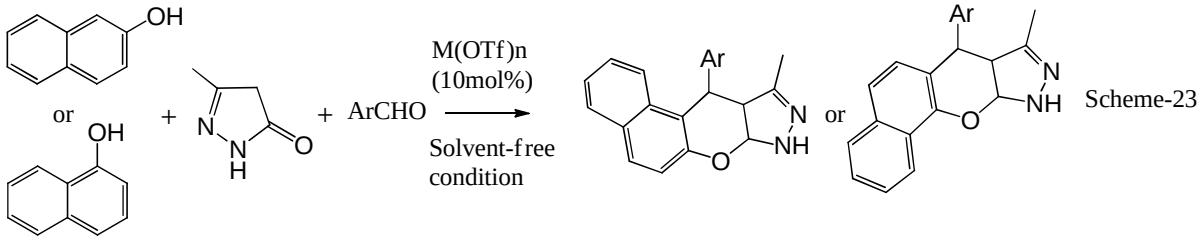
An efficient regioselective synthetic route to multisubstituted pyrazoles by cyclocondensation of β-thioalkyl-α,β-unsaturated ketones with hydrazines was developed by Jin et al[26] (Scheme 22). The reactions of β-thioalkyl-α,β-unsaturated ketones with hydrazines were carried out in the presence of t-BuOK or HOAc in refluxing t-BuOH.



Scheme-22

Reactions Of Pyrazoles:

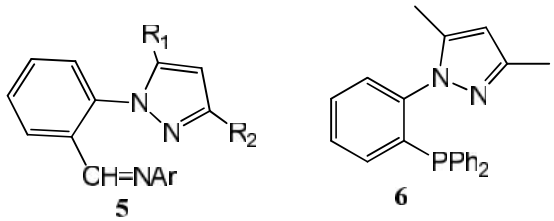
Metal triflates exhibited high efficiency for the synthesis of benzochromeno-pyrazoles. The catalytic efficiency of $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$ and $Cu(OTf)_2$ was studied extensively. In all cases 10 mol% of the catalyst was used and the reaction was carried out under solvent free condition; the best result was obtained when copper(II) triflate. For instance; Damavandi et al[27] developed an efficient and green synthetic route to benzochromeno-pyrazole derivatives via one-pot three component condensation of aldehydes, 3-methyl-1*H*-pyrazol-5(4*H*)-one and α-or β-naphthol catalysed a series of metal triflates under solvent-free conditions at 80°C (Scheme-23).



Scheme-23

Pyrazole- 1*H*-4-carbaldehydes prepared by the Vilsmeier-Haack reaction of phenyl hydrazones were converted into 3-(1,3-diphenyl-1*H*- pyrazol-4-yl) acrylic acids by heating with malonic acid in pyridine and in the presence of catalytic amounts of piperidine. The reduction of pyrazole-1*H*-4-yl-acrylic acids to 3-(1,3-diphenyl-1*H*-pyrazol-4-yl) propanoic acids was carried out using Pd-charcoal and diimide methods[28]. The reduction out by diimide method was found to have advantages of operational simplicity and good yields.

Pyrazole-tethered Schiffs base ligand (**5**) and pyrazole-tethered phosphine ligand (**6**) acts as an efficient catalyst system for Suzuki coupling reactions. For example; in the presence of ligand (**5**), the coupling of aryl bromides/chlorides with phenylboronic acid took place efficiently under mild conditions (Scheme-24)[29]. The catalytic activity depends considerably on the donor atoms and the steric environment around the metal present in the ligand system.



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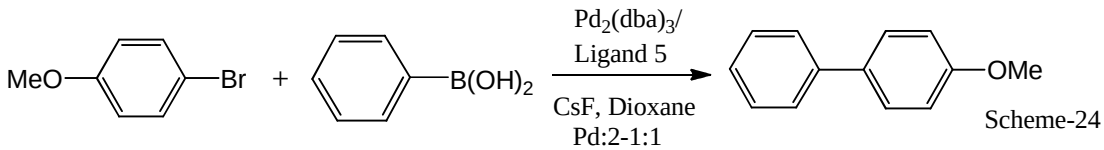
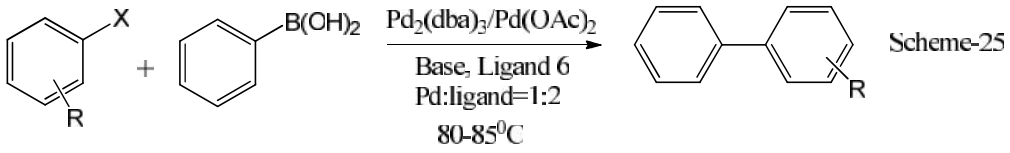


Scheme-24

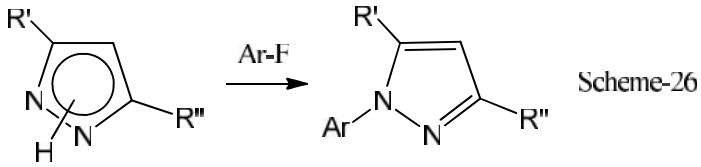
Combination of $Pd_2(dba)_3$ and ligand (**6**) (Pd:6 = 1:2) catalyzed the coupling between aryl bromide and phenylboronic acid at 80-85°C in toluene to produce products in 70-80% yield (Scheme-25)[30].



Scheme-25

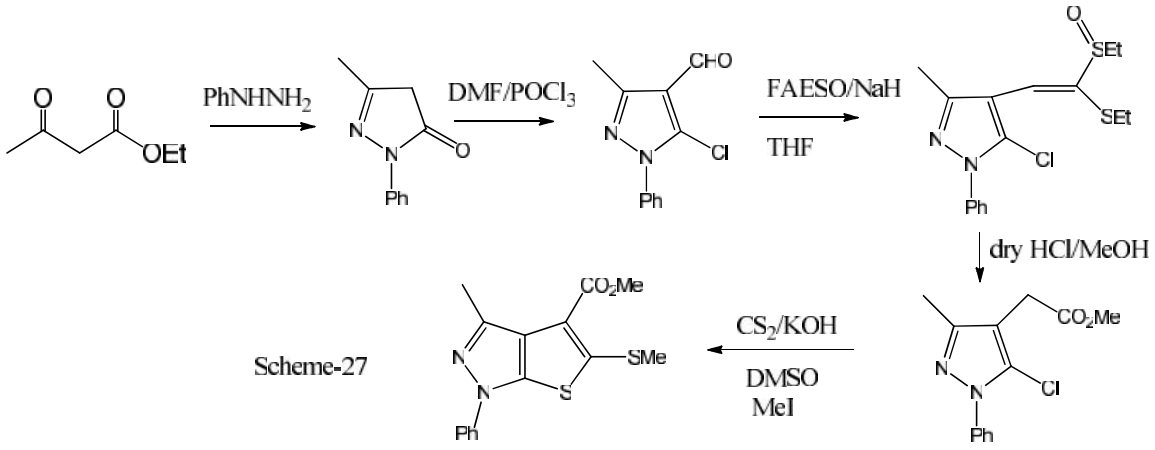
A one pot, mild and efficient method for the synthesis of a series of α-aminophosphonates from pyrazolyl imines and triethyl phosphite using TMSCl as a catalyst by both conventional and under ultrasound irradiation conditions was reported by Deepak and co-workers[31]. Their study revealed that non-conventional method offer advantages over conventional process viz., short time span to complete reaction, easy work procedure and excellent yields.

Ibrahim et al[32] reported the direct *N*-arylation of 3,5-disubstituted-pyrazoles with 4-fluoronitrobenzene and 2-fluoronitrobenzene using potassium tertbutoxide in DMSO using three methods viz., microwave irradiation with or without solvent and a classical heating. The method affords the α-regio isomers in excellent yields (Scheme-26). But in solvent-free under microwave irradiation conditions, the reaction gives a mixture of isomers. The reaction performed without or with some drops of solvent using microwave irradiation increased reaction rates and improved the regioselectivity.



Scheme-26

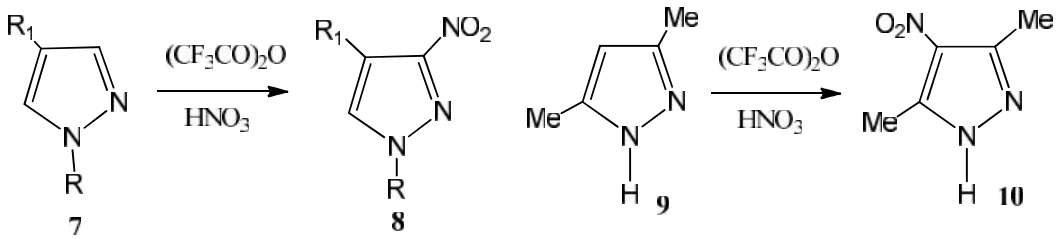
The thermal reactions of 3-methyl-1(2),4,5,6-tetrahydrocyclopenta[*c*]pyrazole under FVP (Flash Vacuum Pyrolysis) conditions. All the products arise from a nitrogen extrusion reaction which proceeds through the different rearrangements of the vinylcarbenes. These intermediates are generated from the two possible tautomeric pyrazoles and can undergo 1,2 or 1,4-H-migration and C-H insertion reactions[33]. Thieno[2,3-*c*]pyrazole was synthesized by the reaction of methyl 4-pyrazoleacetate with carbon disulfide and iodomethane in a new tandem reaction (Scheme-27)[34].



Scheme-27

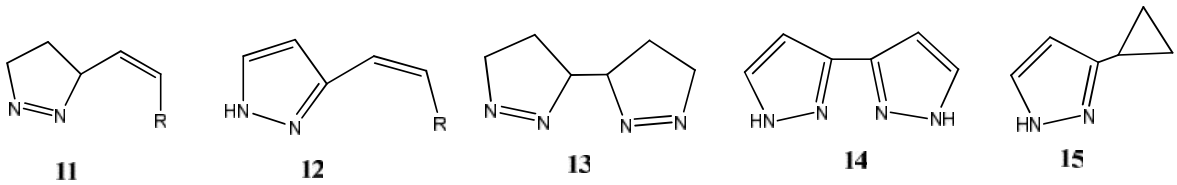
Direct nitration of a variety of pyrazoles with nitric acid/trifluoroacetic anhydride affords mononitro derivatives in average yield of 60 %. Pyrazole (**7**) on treatment with above nitrating system gave a 41% yield of

the 3,4-dinitrated derivative (**8**) while *N*-methylpyrazole under the same reaction condition gave a 65% yield of the 3-nitro product (**8**). 3, 5-Dimethylpyrazole (**9**), on the other hand, gives only 3,5-dimethyl-4-nitropyrazole (**10**) in 76% yield. (Scheme-28)[35].



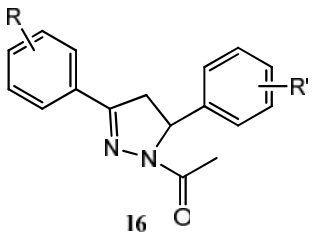
Scheme-28

Oxidative dehydrogenation of 3-vinyl-4,5-dihydro-3*H*-pyrazoles (**11**) with 20eq of MnO_2 in benzene at room temperature to produce 3-alkenyl-1*H*-pyrazoles (**12**) in good yield. While, 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole (**13**) on oxidative dehydrogenation with MnO_2 in benzene at room temperature produces a mixture of 3,3′-bipyrazoles (**14**) and 3-cyclopropyl-1*H*-pyrazole (**15**) in 27 and 18% yield respectively. The 3-cyclopropyl-1*H*-pyrazole (**15**) was presumably formed by the elimination of nitrogen molecule from one dihydropyrazole ring of (**13**)[36].

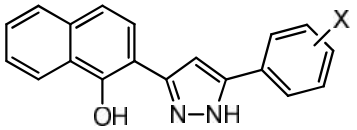


Applications Of Pyrazoles:

Derivatives of pyrazoles have played a crucial role in the history of heterocyclic chemistry and been used as important pharmacores and synthons in the field of organic chemistry and drug designing. A series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazoles (**16**) synthesised were investigated for their ability to inhibit selectively monoamine oxidases, swine kidney diamine oxidase (SKDAO) and bovine serum amine oxidase (BSAO). These compounds were reversible and non-competitive inhibitors of all types of the assayed amine oxidases. In particular 1-acetyl-3-(2,4-dihydroxyphenyl)-5-(3-methylphenyl)-4,5-dihydro-(1H)-pyrazole showed I50 values of 40nM accompanied by a selectivity factor of 4000 for MAOs (mitochondrial monoamine oxidases). By replacing the substituted phenyl ring at N_1 by an acetyl group increased the inhibitory activity and selectivity towards MAOs of pyrazoles likely taking part in the interaction with the isoalloxazine nucleus[37].



2-(5-Substituted-1*H*-pyrazol-3-yl) naphthalen-1-ol derivatives (**17**), a non vicinal diaryl heterocycle synthesised were evaluated for *in-vivo* anti-inflammatory activity by acute carrageenan induced paw edema standard method in rats using Indomethacin as a standard drug. The compounds containing electron donating methyl and halogen functional group showed more activity than that of electron withdrawing nitro and dinitro functional group[38]. A series of nine tetrasubstituted pyrazolines (**18**) synthesised by 1,3-dipolar cycloaddition of aromatic aldehyde phenyl hydrazones and cinnamonitrile with chloramine-T as catalytic dehydrogenating agent have showed promising antifungal, antibacterial and antioxidant activities[39].



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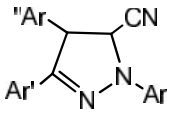
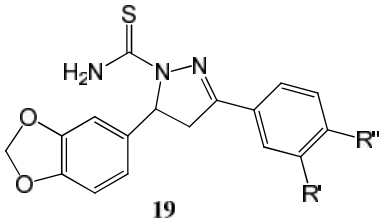


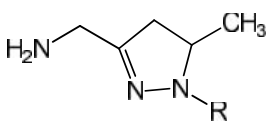
18

The anticancer activity of the pyrazole analogues of piperine (**19**) were determined by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-di phenyl tetrazolium bromide) assay method. The anti inflammatory activity of the compounds (**19**) was determined by Human Red Blood Cell (HRBC) membrane stabilization method at doses of 100 µg, 500 µg and 1000 µg. These analogues also showed good binding affinity with Cycloxygenase and farnasyl transferase receptors, which was proved from the docking studies[40].



19

1-(5-Methyl-4*H*-pyrazol-3-yl)methanamine derivatives (**20**) [41] synthesised showed significant antibacterial activity when compared to the standard drug. Trisubstituted pyrazolines (**21**)[42] obtained by one pot route have exhibited promising antifungal activities against different organism.



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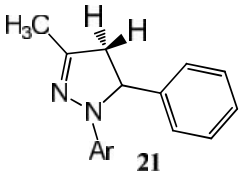
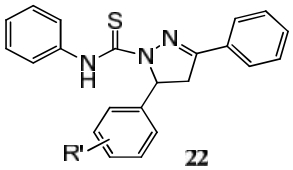


21

Pyrazole derivatives (**22**)[43] synthesized were screened for anti-tubercular activity. The minimal inhibition concentration was used to evaluate the anti-tuberculosis activity. Shin-Ru-Shih et al[44] reported that BPR1P0034 (**23**) has potent inhibitory activity against influenza virus. They showed that BPR1P0034 is the first pyrazole-based anti influenza compound ever identified and characterized from high through put screening to show potent (sub-µM) antiviral activity.



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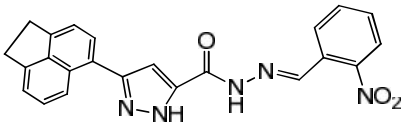
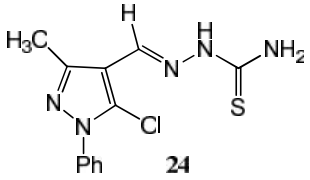


23

Abdel Hameed and co-workers[45] reported 5-chloro-1-phenyl-3-methyl-pyrazolo-4-methinethiosemicarbazone (**24**) as corrosion inhibitors for carbon steel in 1M HCl by chemical and electrochemical method. The corrosion rate decreased and inhibition efficiencies and surface coverage degree increased with increasing in inhibitor concentration and temperature. The protective film of these compounds formed on the carbon steel surface is stable at higher temperature. Nitulescu and co-workers[46] synthesized N-(1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives (**25**) and evaluated for their analgesic and sedative effects. The compounds showed promising activities.



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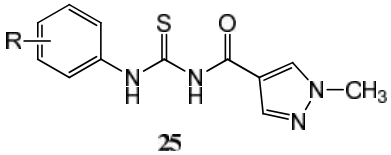
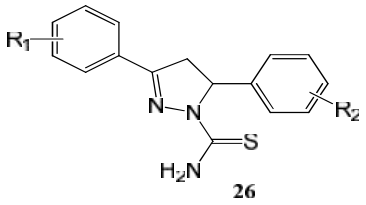


25

The synthesis and structure–activity relationship of pyrazole derivatives (**26, 27**) as anticancer agents that may function as inhibitors of EGFR and kinases was reported. Some of them exhibited significant EGFR inhibitory activity. 3-(3,4-Dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**26**) displayed the most potent EGFR inhibitory activity with IC50 of 0.07 lM, which was comparable to the positive control erlotinib. The compound also showed significant antiproliferative activity against MCF-7 with IC50 of 0.08 lM and potent inhibitory activity in tumor growth inhibition[47].



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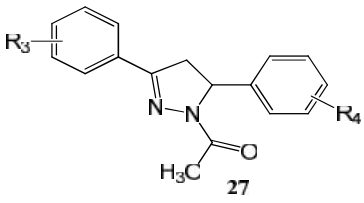

27

Conclusion:

Pyrazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are discussed in brief in this article. This article mainly focused on the synthetic strategies and biological activities associated with pyrazoles. Although organic chemists devised a broad range of methods for the synthesis of pyrazoles and new methods continue to appear, the design of new regioselective pyrazole forming reactions is still a compelling research topic. It is the fact that pyrazole derivatives are important compounds for biological systems, medicines, agrochemicals and many fields of industrial products. This review become a basis and is useful for researchers to device a new synthetic approach, new molecules of biological potency.

Authors Contributions: All authors involved in collection of data, manuscript preparation and read and approved the article.

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