PYRAZOLES IN MEDICINAL CHEMISTRY

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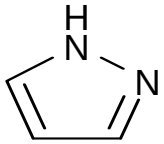
Summary

Pyrazole a five membered heterocyclic system consisting of three carbon atoms and two nitrogen atoms shows wide range of biological activities. Certain drug like Flucanozole, Ketoconazole etc. posses's pyrazole ring and shows promising anti fungal activity. First time it is synthesized from chalcones using Pechmann reaction. It can also be prepared by cycloaddion reactions of hydrazine's and substituted chalcones. In medicine, pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities etc.The present reviews attempted to gather the various developments in synthesis and biological activities of pyrazole derivatives.

Key words: Pyrazole, Pharmacological activity, Regioselective synthesis, SAR, Total synthesis**.**

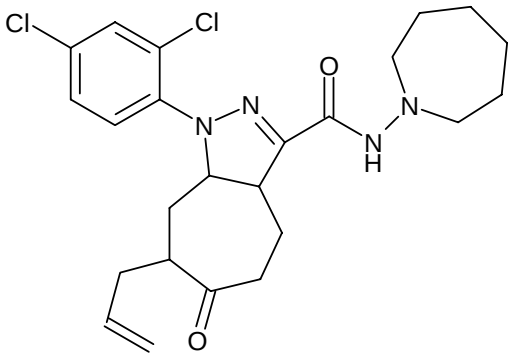
Introduction

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature.[1]
It was first time synthesized by H. Pechmann in 1898 from acetylene and diazomethane.[2]
In medicine, pyrazoles are used for their analgesic, anti-inflammatory, antipyretic,antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities.



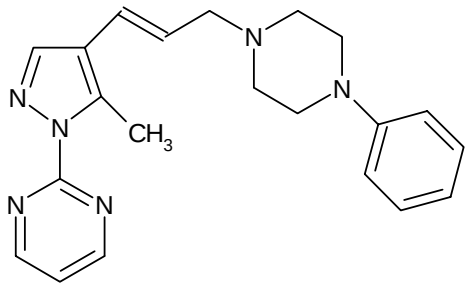
Cannabinoid CB1 Receptor Antagonists

The design, synthesis and biological activities of potent pyrazole-based tricyclic CB1 receptor antagonists are described. The key synthetic step involves the ring closure of the lithiated a,g -keto ester adduct. The optimal nitro derivative in this series exhibits a high CB1 receptor affinity (p*K*i57.2) as well as very potent antagonistic activity (p*A*258.8) *in vitro*. The regioselectivity of the pyrazole ring closure is shown to depend strongly on the aromatic substitution pattern of the applied aryl hydrazine.[3]

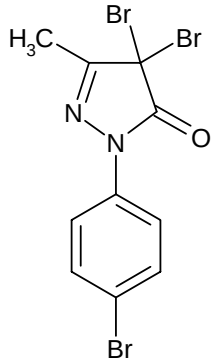


Antitumor Activity

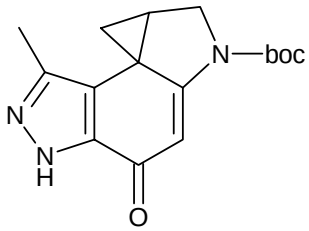
1. A series of novel 3-substituted-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-propenes in order to improve the *in vitro* and *in vivo* activity of our prototype 3-[4-(3-chlorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-ropene were synthesized and evaluated by assays of growth inhibition against several tumor cell lines *in vitro* and antitumor activity against some tumor models when dosed both intraperitoneally and orally *in vivo*. Compounds 7a and 7e, the 3,5-difluorophenyl and 3,5-dichlorophenyl analogues showed significantly more potent cytotoxicity than 2 *in vitro* and potent antitumor activities without causing decrease of body temperature related to side effects.[4]



2. Derivatives of 5-methyl-2,4-dihydro-pyrazol-3-one, 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one and 2-(2,4-dinitro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one have been brominated in various ways. The compounds were synthesized by condensation reaction between the ethylacetoacetate and hydrazine derivatives. All the products have been characterized by extensive use of **IR**, **^{1}H-NMR**, **^{13}C-NMR** and **Mass** spectral analysis. Investigation of the cytotoxicity of these compounds was carried out against brine shrimp by lethality bioassay. The cytotoxicity studies of the synthesized compounds revealed that compound 4,4-dibromo-2-(2,4-dinitro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one had shown tremendous bioactivity against brine shrimp. However, the compounds 4,4-dibromo-5-methyl-2,4-dihydro-pyrazol-3-one,4,4-dibromo-2-(2,4-dibromo phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one and 4,4-dibromo-2-(dinitro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one showed higher activity leaving the other compounds almost inactive.[5]

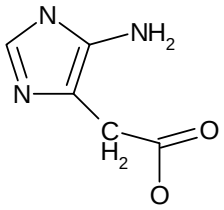


3. These hybrid compounds have obtained coupling of the two *N*-Boc deprotected CPI pyrazole analogs with three mixed pyrazole–pyrrole compounds called lexitropsins (or information-reading oligopeptides), consisting of a varying number of pyrrole amide units (from one to three) tethered on the *N*-terminus to a 3,5-pyrazole dicarboxylic acid moiety, and structurally related to the DNA minor-groove binder distamycin A .it was found that tethering the pyrazole CPI analogs to the DNA-binding lexitropsins afforded, with few exceptions, conjugate molecules that showed enhanced cytotoxic activity against five different cancer cell lines in vitro.[6]



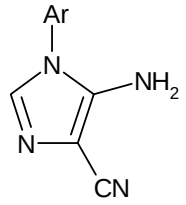
***Helicobacter Pylori* Urease Inhibitors**

A computer-generated homology model of the antimicrobial target *Helicobacter pylori* urease was derived, using the x-ray crystal structure of *Klebsiella aerogenes* as a template, in order to design novel urease inhibitors. Based on these computational studies, several heterocyclic hydroxamic acid derivatives have been designed, synthesized, and examined for their ability to inhibit urease activity.[7]

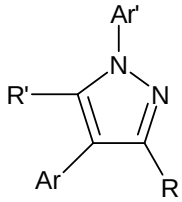


Antimicrobial activity

1. 6-Dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11-yl)-hydrazine (**1**) was used as a precursor for preparation of some novel 1-(5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11-yl)-pyrazole derivatives **2-7**. Also, some acyclic and cyclic *C*-nucleosides were prepared by treating compound with aldoses. Some of the prepared products showed potent antimicrobial activity.[8]

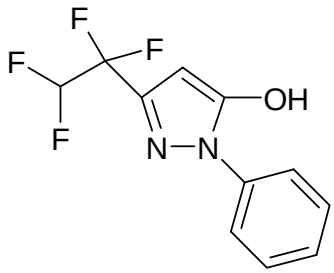


2. Hydrazonyl bromides reacted with active methylene compounds (dibenzoylmethane, acetylacetone, ethyl acetoacetate, phenacyl cyanide, acetoacetanilide, ethyl cyanoacetate, cyanoacetamide and malononitrile) to afford the corresponding 1,3,4,5- tetrasubstituted pyrazole derivatives . Reaction of with formamide, formic acid and triethyl orthoformate give the pyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-*d*]pyrimidin-4(3H)one and 5-ethoxymethylene-aminopyrazole-4-carbo-nitrile derivatives. Compounds reacted with benzhydrazide and hydrazine hydrate to afford pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine and [4-iminopyrazolo- [3,4-*d*]pyrimidin-5-yl]amine derivatives. Reactions of compounds with triethyl orthoformate and carbon disulfide give the corresponding pyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine derivatives.[9]



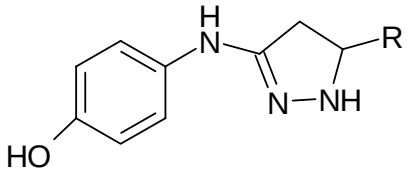
Anxiolytic activity

New anxiolytics have been discovered by prediction of biological activity with computer programs PASS and DEREK for a heterogeneous set of 5494 highly chemically diverse heterocyclic compounds (thiazoles, pyrazoles, isatins, a-fused imidazoles and others). The majority of tested compounds exhibit the predicted anxiolytic effect. The most potent activity was found in 2-(4-nitrophenyl)-3-(4-phenylpiperazinomethyl)imidazo[1,2-a]pyridine 8, 1-[(4-bromophenyl)-2-oxoethyl]-3-(1,3-dioxolano)-2-indolinone 3, 5-hydroxy-3-methoxycarbonyl-1-phenylpyrazole and 2-(4-fluorophenyl)-3-(4-methylpiperazinomethyl)imidazo[1,2-a]pyridine. The application of the computer-assisted approach significantly reduced the number of synthesized and tested compounds and increased the chance of finding new chemical entities (NCEs).[10]



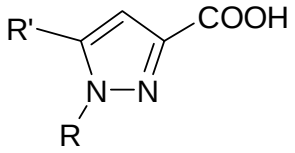
Analgesic and Anti-inflammatory activity

An attempt has been undertaken for the synthesis of the some novel 4-(5_substituted aryl-4_, 5_-dihydropyrazole-3_-ylamino) phenols possessing potent biological activities. The synthesized compounds were tested for their possible analgesic, anti-inflammatory and anti-microbial activities.[11]



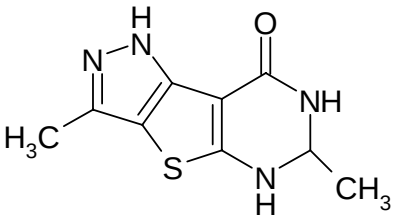
Inhibitors of ALK5

Ten new 1, 5-diarylpyrazole-3-carboxamide compounds were synthesized and their structures were identified by ^{1}H-NMR and FAB-MS. The primary biological tests showed that compound 4j exhibited some ALK5 inhibitory activity at concentration of 1μmol/L. [12]



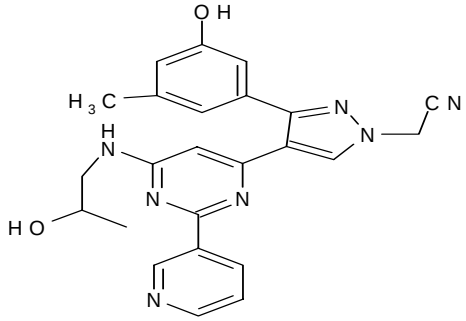
Antitubercular activity

A new synthetic route is proposed for the synthesis of 3,6-dimethyl-6-aryl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones from 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile **.** Synthesis of the key compound was accomplished via a Gewald reaction. The newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic investigation. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}RV$. [13]



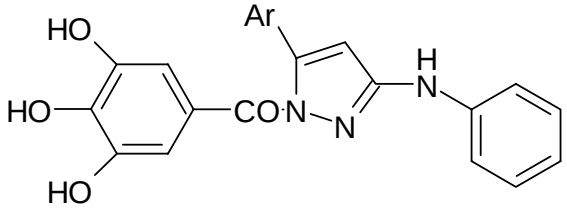
Selective ROS1-tyrosine kinase inhibitor

ROS1 protein is a receptor tyrosine kinase that has been reported mainly in meningiomas and astrocytomas, and until now, there is no selective inhibitor for this kinase. In this study, we illustrate for the synthesis of a highly potent and selective inhibitor for ROS1 kinase. The synthesized compound 1 was tested initially at a single dose concentration of 10 lM over 45 different kinases. At this concentration, a 94% inhibition of the enzymatic activity of ROS1 kinase was observed, while the inhibition in activity was below 30% in all of the other kinases. The pyrazole compound 1 was further tested in a 10-dose IC50 mode and showed an IC50 value of 199 nM for ROS1 kinase. The compounds can be used as a promising lead for the development of new selective inhibitors for ROS1 kinase, and it may open the way for new selective therapeutics for astrocytomas.[14]



Anti-inflammatory Activity

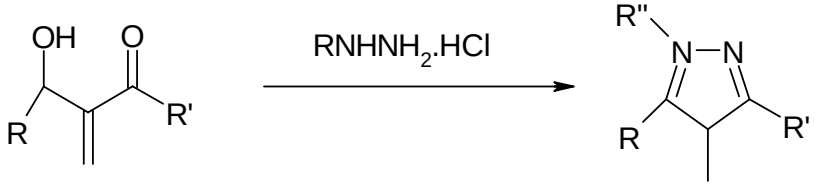
In the present study, a new series of [5-substituted-3-(phenylamino)-1*H*-pyrazol-1yl] (3,4,5-trihydroxyphenyl)-methanone have been synthesized. 3, 4, 5-Trihydroxy benzohydrazide was synthesized from propyl gallate and hydrazine hydrate in presence of ethanol. Chalcones were synthesized from acetanilide and various aromatic aldehydes in presence of ethanol and sodium hydroxide solution. By refluxing the compound and compounds in presence of ethanol yielded [5-substituted-3-(phenylamino)-4.5-dihydropyrazol-1yl] (3,4,5-trihydroxy phenyl)-methanone. The final compounds [5-substituted-3-(phenylamino)-1*H*-pyrazol-1yl] (3,4,5-trihydroxyphenyl)- methanone were synthesized by treating compounds with bromine water. The synthesized compounds have been characterized by IR, 1HNMR and Mass spectral data. The compounds were evaluated for *in vivo* anti-inflammatory activity by carrageenan induced paw edema test. In general all compounds were found to exhibit good anti-inflammatory activity.[15]



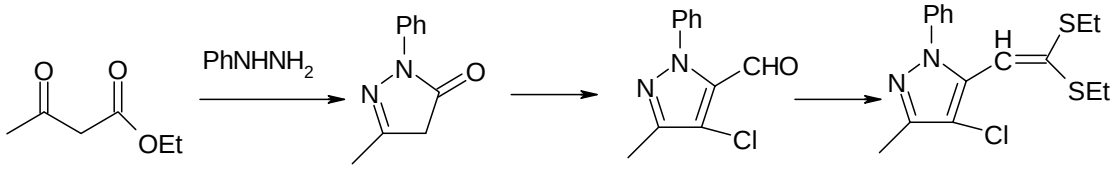
Methods of synthesis

1. Recently we have reported on the regio-selective synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives from the reaction of Baylis-Hillman adducts of alkyl vinyl ketone and hydrazine derivatives. During the continuous studies on the chemical transformations of Baylis-Hillman adducts 6,7 including the synthesis of pyrazoles2 we presumed that we could synthesize 1,3,4-trisubstituted

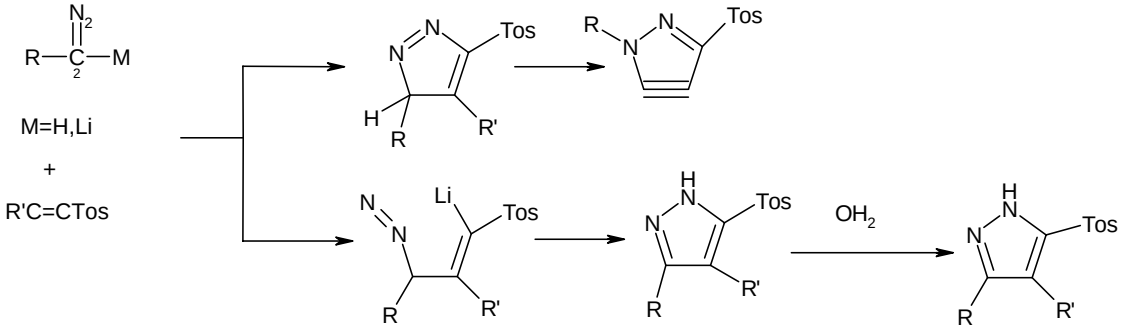
pyrazoles from the reaction of hydrazine derivatives and acyloxiranes,which could be synthesized easily from Baylis-Hillman adducts.[16]



2. A new method was found for the synthesis of pyrazoleacetate esters from pyrazolaldehyde. By a new tandem reaction, in which methyl 4-pyrazoleacetate reacted with carbon disulfide and iodomethane, thieno[2,3-c]pyrazole was synthesized. This was an easy method for the synthesis of this type of heterocycles.[17]

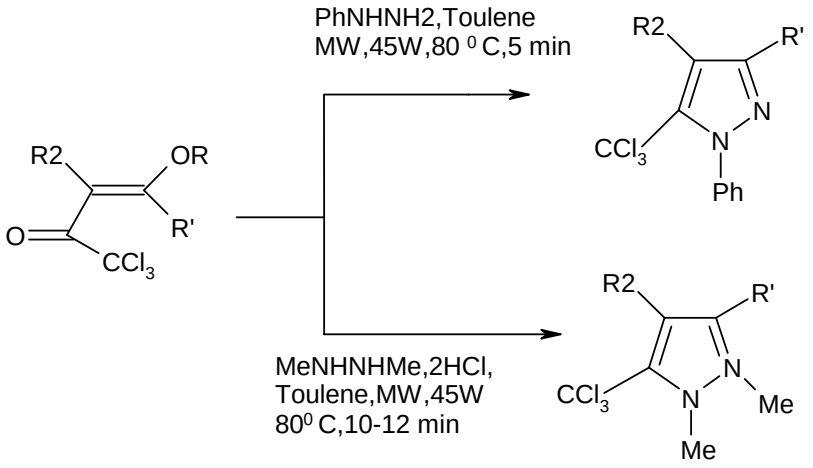


3. Due to their 1,3-dipolar structure, diazoalkanes (RR'CN2) have been extensively used for the synthesis of various five-membered heterocycles. In this field, metalated diazo derivatives [R(CN2)M] have been used as *activated* diazoalkanes and for instance, numerous azoles have been prepared by reacting the lithium salt of the trimethylsilyldiazomethane [Me3Si(CN2)Li] with nitriles, carboxylic esters, carbamoyl- and thiocarbamoylchlorides. It is noteworthy that we have demonstrated that metalation of diazo derivatives affords ambident and highly functionalized nucleophiles that can react either *via* the carbon atom leading to new diazo derivatives or *via* the terminal nitrogen giving nitrile-imines. Here we report for the first time that lithiation of diazo derivatives can dramatically modify the course of their reaction with electron-poor alkynes.[18]

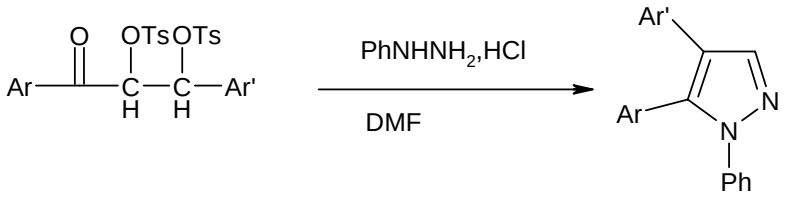


4. A series of five 5-trichloromethyl-1-phenyl-1*H*-pyrazoles and six 5-trichloromethyl-1,2-dimethylpyrazolium chlorides have been synthesized in 80–98% yield by environmentally benign microwave induced techniques involving the cyclocondensation of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones [Cl3C(O)C(R2)=C(R1)OR, where R2=H, Me; R1=H, alkyl, phenyl and R=Me, Et] with phenyl hydrazine and 1,2-dimethylhydrazine dihydrochloride,

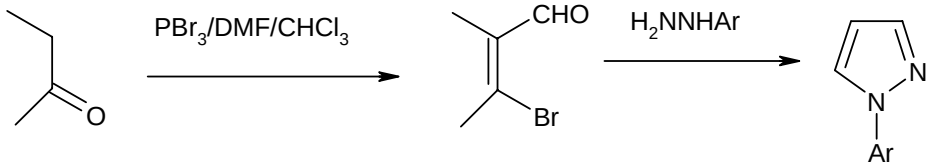
respectively, using toluene as solvent. The use of microwave and classical methods are comparable for making pyrazoles, but the formation of pyrazolium chlorides can be achieved in a significant shorter time, and in some cases better yield. [19]



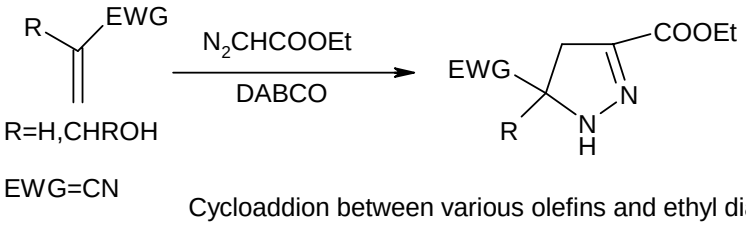
5. The reaction of a,b-chalcone ditosylates with various reagents such as phenylhydrazine hydrochloride, semicarbazide hydrochloride and thiosemicarbazide in suitable conditions leads to 1,2-aryl shift, thereby providing a novel route for the synthesis of 1,4,5-trisubstituted pyrazoles.[20]



6. Cyclic and acyclic b-bromovinyl aldehydes are cyclized with an array of arylhydrazines in toluene at 125 _C in the presence of a palladium catalyst and a phosphorus chelating ligand together with NaOtBu to give 1-aryl-1H-pyrazoles in moderate to good yields. [21]

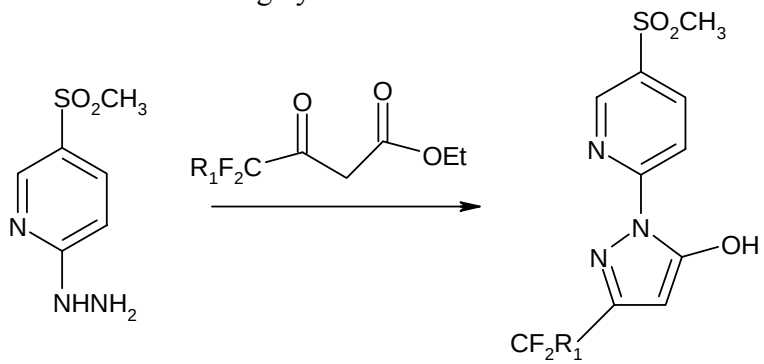


7. A facile, InCl3 and/or DABCO mediated 1, 3-dipolar cycloaddition of ethyl diazoacetate (EDA) with various activated olefins under solvent-free conditions at ambient temperature to afford 3, 5-disubstituted pyrazolines and pyrazoles in moderate to good yields is reported. [22]

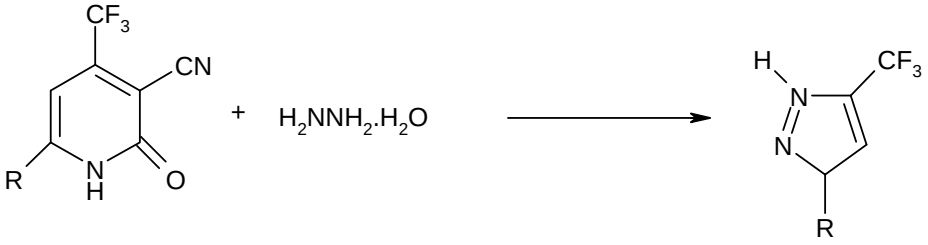


Cycloaddion between various olefins and ethyl diazoacetate

8. Fluoride-mediated nucleophilic substitution reactions of 1-(4-methylsulfonyl (or sulfonamido)-2-pyridyl)-5-chloro-4-cyano pyrazoles with various amines and alcohols occur under mild conditions to provide the 5-alkyl amino and ether pyrazoles in moderate to high yields. [23]

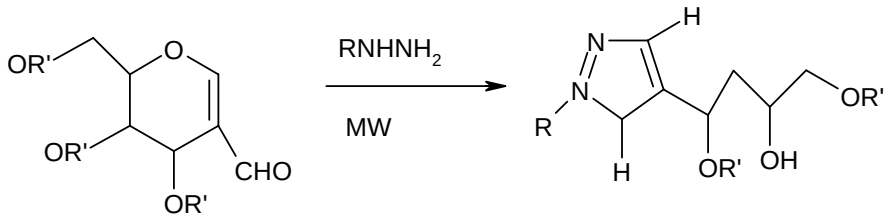


9. The 3-cyano-4-trifluoromethyl-6-phenyl or substituted phenyl 2(1H) pyridones on reaction with hydrazine hydrate, gave exclusively in 5-trifluoromethyl-3-substituted pyrazoles through a novel method. A possible mechanistic pathway for change in the site of nucleophilic attack due to the CF3 group in 2(1H) pyridones is described.[24]



R=C_6H_5,p-$CH_3C_6H_4$,p-ClC_6H_4

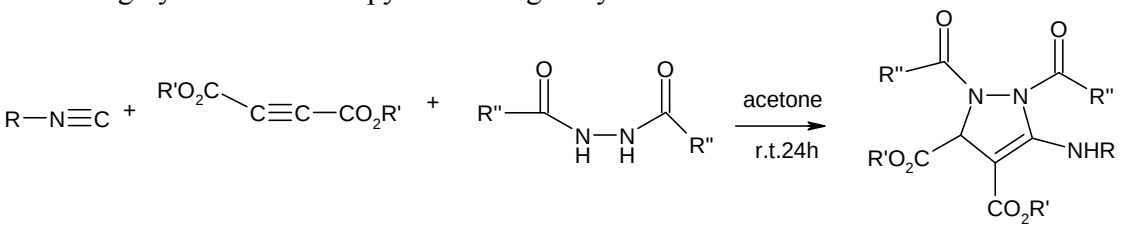
10. 2-Formyl glycals undergo rapid condensation with arylhydrazines under solvent-free conditions to give the corresponding optically pure 4-substituted pyrazoles in good yields with high selectivity. The stereochemistry of the products was assigned by various NMR experiments.[25]



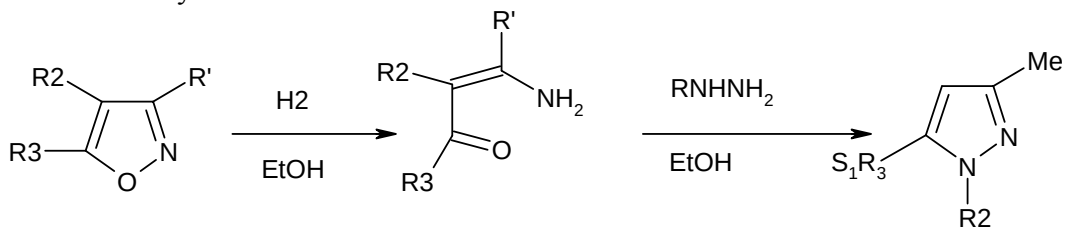
R= Aryl or H

R'= Bn,Et,Me

11. The reactive 1:1 intermediate produced in the reaction between isocyanides and dialkyl acetylenedicarboxylates was trapped with 1,2-diacylhydrazines to yield highly functionalized pyrazoles in good yields.[26]



12. Silyl b-enaminones have been synthesized by reductive cleavage of 5-silyl, 3-, 4- and 5-silylmethylisoxazoles.These versatile synthons bearing different silyl groups in various positions of the enaminoketonic system are of great interest in the regioselective synthesis of 3- or 5-silylpyrazoles and 3-, 4- or 5-silylmethylpyrazoles, which can serve as building blocks in heterocyclic chemistry. [27]



Conclusion

1-*H*-Pyrazole a novel heterocycle possessing various biological activities like anti fungal, antimicrobial, antitubercular, antipsychotic activities. The methods of synthesis are also simple. Thus it can be proved as promising agents for medicinal chemists to synthesize various new chemical entities having desired biological activities.

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