

REVIEW OF PYRAZOLE COMPOUNDS' PRODUCTION, USE, AND PHARMACOLOGICAL ACTIVITY

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Abstract

The pharmacologically significant active scaffold pyrazole and its derivatives are thought to have practically all pharmacological actions. The pyrazole moiety's pharmacological potential has been demonstrated by the presence of this nucleus in pharmacological agents from a variety of therapeutic categories, including the powerful anti-inflammatory celecoxib, CDPPB, an antipsychotic, and rimonabant, a weight-loss medication, the analgesic difenamilole, Betazole, an H₂-receptor agonist, and an antidepressant fezolamide. This nucleus has drawn the interest of numerous researchers who are studying its skeleton chemically and physiologically because of its diversity in the biological area. The various production techniques and the pharmacological characteristics of pyrazole derivatives are highlighted in this review. It is said that numerous scientists from all over the biological sciences have been studied over the globe. Activity and synthesis numerous derivatives of pyrazoles.

Keywords: Biological Activity, Synthesis, Reaction, and Pyrazole.

1. INTRODUCTION

One class of molecules that is very useful in the synthesis of organic compounds are five-membered heterocycles, or pyrazoles. They are among the chemical categories of the azole family that have been studied the most. In actuality, a wide range of various synthesis methods and synthesizing, analogs have been documented.

Due to their fascinating pharmacological properties, pyrazole complexes have received more attention as biomolecules. Numerous well-known drugs from a variety of therapeutic categories and categories can include this heterocycle and have a variety of therapeutic effects. [1, 2]. We describe and discuss the most pertinent synthetic techniques and pharmacological characteristics of heterocyclic systems produced from pyrazoles in this review.

2. THE PRIMARY ACCESS TECHNIQUES TOWARDS THE PYRAZOLE NUCLEUS

Extravagant aromatic heterocycle is pyrazole. Position 4 is the preferred site for electrophilic substitution reactions, whereas Positions 3 and 5 are the preferred sites for nucleophilic assaults. This section will discuss analyze this evolution and describe the techniques typically employed to obtain replaced pyrazoles, that is to say:

1. Hydrazine and related compounds undergo cyclocondensation with carbonyl systems.
2. Cycloadditions with two poles.
3. Multi-participant reactions.

2.1 Derivatives of hydrazine Cyclocondensation relating to 1,3-Difunctional Systems

A 1, 3-dicarbonyl molecule, one, three-dicarbonyl derivative, or a ketone that is, -unsaturated are suitable carbon units for a process of Cyclocondensation between a suitable hydrazine acting as a bidentate nucleophile, Figure (1).

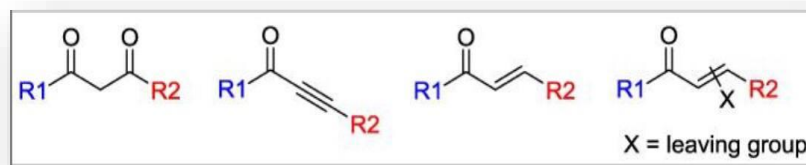
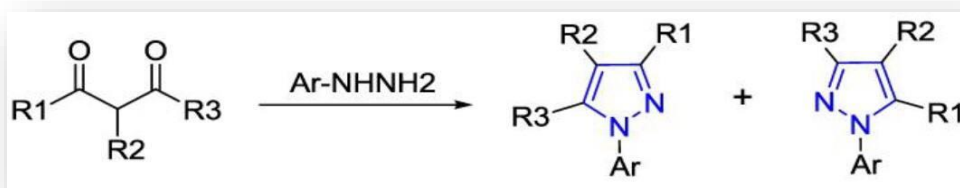


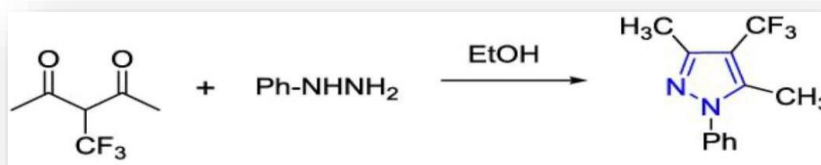
Figure 1: Compounds with α , β -unsaturated carbonyl

2.1.1 From 1, 3-Diketones, A quick and easy way to create polysubstituted pyrazoles is to cyclocondensate 1, 3-dicarbonyl substances with hydrazine derivatives. By reacting -diketone with hydrazine derivatives, Knorr et al.[3] carried out the initial production of substituted pyrazoles in 1883, yielding two regioisomers, **Scheme (1)**.



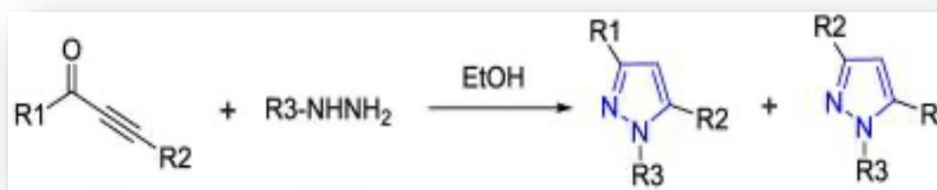
Scheme 1: 1, 3-Dicarbonyl compounds are created during the synthesis of polysubstituted pyrazoles.

Similar to this, Ohtsuka et al. [4] investigated the phenylhydrazine condensation and 2-(trifluoromethyl)-1, 3-diketone in ethanol, resulting in the good yield (63% yield) of 1, 3, 4, 5-substituted pyrazole. Because the sterically tiny More nucleophilic than NHPH is NH_2 , compound 8 was the only one to form, **Scheme (2)**.



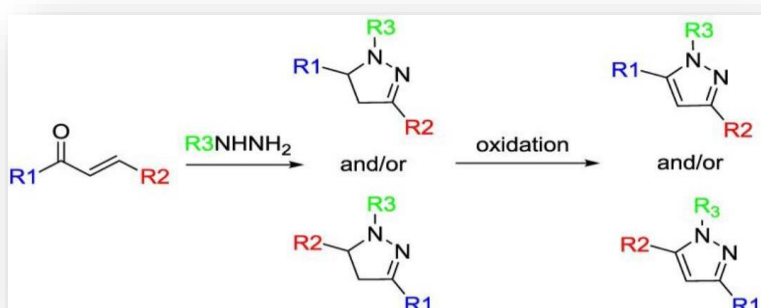
Scheme 2: From 2-(trifluoromethyl)-1, 3-diketone, 1, 3, 4, 5-substituted pyrazoles are synthesized

2.1.2 From Acetylenic Ketones, More than a century has passed since the discovery of the reaction of Cyclocondensation between derivatives of hydrazines and acetylenic ketones to produce pyrazoles [5]. But once more, the amalgam of the a pair of regioisomers, **Scheme (3)**.



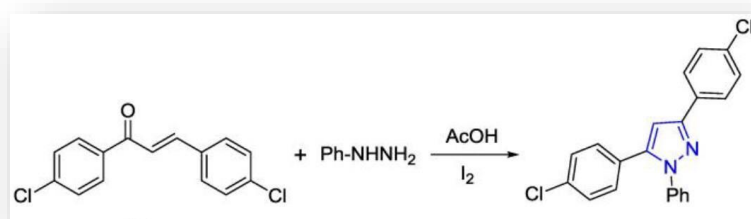
Scheme 3: Pyrazole Synthetic process using acetylenic ketones

2.1.3 From Vinyl Ketones a hydrazine derivative and an ethylenic ketone undergo Cyclocondensation to create pyrazolines, which are then oxidized to produce the pyrazole ring **Scheme (4)**.



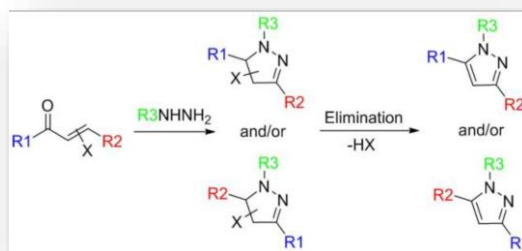
Scheme 4: Pyrazole Preparation from Cyclocondensation of, α , β -ethylenic ketone

Similar to this, a process was described for creating Trisubstituted 1, 3, and 5 pyrazoles from an, α , β -ethylenic ketone. The corresponding pyrazole was produced in good yield (70%) by cyclocondensing the phenylhydrazine and the, α , β -ethylenic ketone (1.2 eq.) 5 in acetic acid and iodine are present. (1.0 eq.), [6], **Scheme (5)**.



Scheme 5: By using the Cyclocondensation process from α , β -ethylenic ketone, pyrazoles are synthesized

2.1.4 Derived from vinyl ketone, Leaving with a Group If the leaving group is removed from the, α , β -ethylenic ketones, they can combine with hydrazine derivatives. to produce in which pyrazolines then give the required pyrazoles **Scheme (6)**.

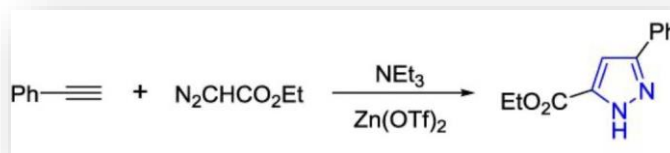


Scheme 6: By Cyclocondensing, α , β -ethylenic ketones with Pyrazoles, a departing group are created

2.2. The 1, 3-Dipolar Cycloaddition:

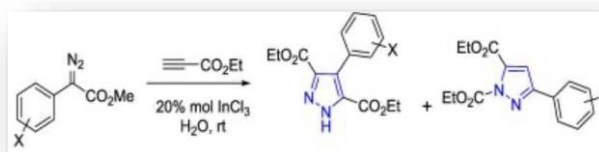
The Alkyne and [3 + 2] cycloaddition reactions and 1, 3-dipolar substances like the sydrones, nitrilimines, or diazo compounds provide another approach for gaining reaching the pyrazole nucleus.

2.2.1 Diazocarbonyl compound cycloaddition He and colleagues [7] looked into the 1, 3-dipolar cycloaddition reaction that occurs when α - ethyl diazo acetate reacts with phenylpropargyl whenever zinc triflate is present as a catalyst in triethylamine. The resulting pyrazole is produced in a good yield (89%). This approach has the potential to be helpful in organic synthesis due to its clear process, straightforward reaction conditions, synthetically valuable compounds, good yielding, and ease of manipulation, **Scheme (7)**.



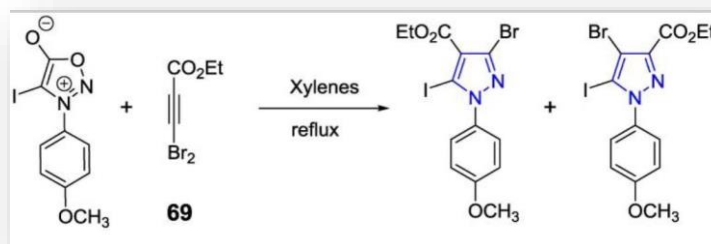
Scheme 7: Through a 1, 3-dipolar cycloaddition of α - ethyl diazo acetate, pyrazoles are created

Two regioisomers were produced under the identical circumstances when different aryl α -diazoarylacacetates reacted with methyl propionate. Minor compounds (4–12%) are produced by the ester group migrating to the nitrogen atom following cyclization. The group of aryl would move to the nearby atomic carbon, then rearranging prototropically would result in the majority compound (77-90%), **Scheme (8) [8]**.



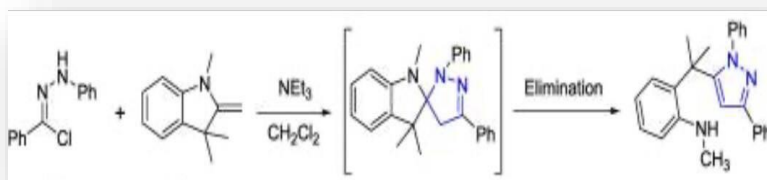
Scheme 8: Utilizing 1, 3-dipolar cycloaddition of α -diazoarylacacetates for the synthesis of pyrazoles

2.2.2 A Sydnone A pyrazole is can be produced by cycloaddition of synthetic nones. The two 1, 3, 4, and 5-substituted pyrazoles are regioisomeric. were synthesized by Delaunay and colleagues employing the cycloaddition of an alkyne and a sydnone. Within 15 hours, the reaction was finished, producing a 3:1 regioisomeric 5-iodopyrazole combination in an 84% overall yield. The intended main isomer (63% isolated yield) was assigned a structure based on the 1H-NMR spectra after the Silica gel chromatography made it simple to separate pyrazoles, **Scheme (9)[9]** .



Scheme 9: By using an alkyne and sydnone cycloaddition procedure to create pyrazoles

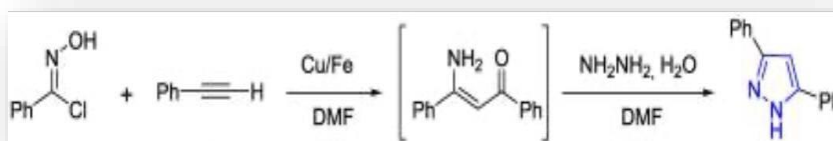
2.2.3 Nitrilimines, triethylamine is present in dichloromethane, Dadiboyena et al. reported diphenylnitrilimine's 1, 3-dipolar cycloaddition to an alkene. to produce 1,3,5-trisubstituted pyrazole. Only available item other than the anticipated spiro-pyrazoline was the trisubstituted pyrazole, which was isolated in 88% yield, **Scheme (10) [10]**.



Scheme 10: Diphenylnitrilimine and an alkene undergo 1, 3-dipolar cycloaddition to produce pyrazole

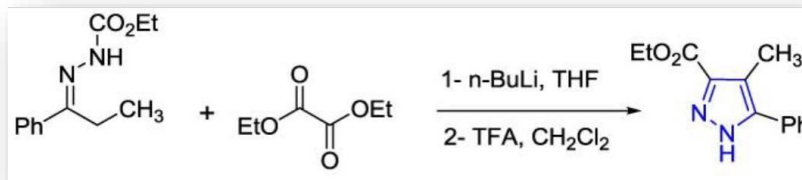
2.3 Multicomponent Methodologies

(2.3.1) in situ synthesis of β -Amino enones, through the use of a unique method called Alkyne-oxime coupling in dimethylformamide under the influence of cupro, Kovacs et al. were able to create 3,5-substituted pyrazoles. The precious β -amino enone was converted into pyrazoles in combination with hydrazine, and the product was separated with a 70% yield, **Scheme (11) [11]**.



Scheme 11: 3, 5-Diphenylpyrazole synthesis by combining alkyne and oxime with a cuprocatalyst.

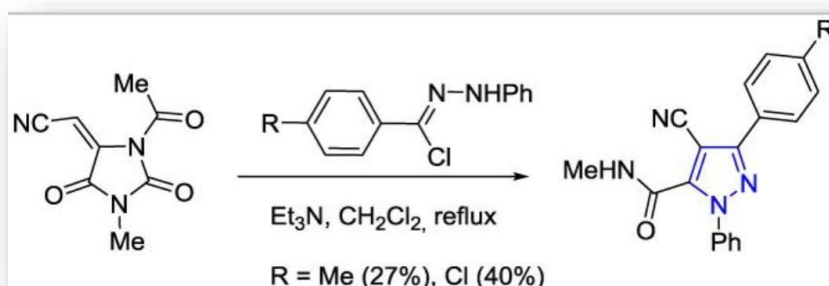
2.3.2 Hydrazone Formation in situ, Section According to Dang et al. a unique process for the one-pot cyclization for hydrazone dianions using diethyl dioxalate to produce pyrazole-3-carboxylates. Diethyl oxalate was cyclized with hydrazone dianions to produce pyrazole-3-carboxylates in good yields (53%) Scheme (12) [12].



Scheme 12: Hydrazone cyclization in a single pot using diethyl dioxalate to produce pyrazoles

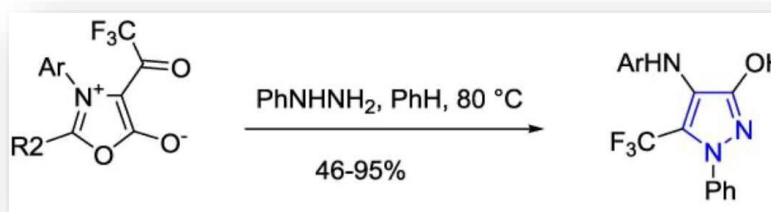
2.4 From Heterocyclic Systems

2.4.1 Using imidazole (5Z) cycloaddition-1-acyl-5-(cyanomethylidene)-3-methylimidazolidine Under basic conditions, 4,2-diones and Chloride of Arylhydrazonyl yield pyrazole-5-carboxamides with a reasonable yield of 27–40%, **Scheme (13)** [13].



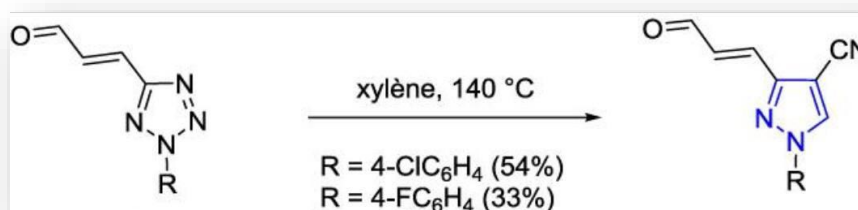
Scheme 13: Pyrazole synthesis from oxazoles.

2.4.2 Heating phenylhydrazine from oxiazoles and 5-oxazolium-4-trifluoroacetyl-1,3-diolates under benzene reflux produced excellent yields of 5-trifluoromethyl-3-hydroxypyrazoles (46-95%), Scheme (14) [14].



Scheme 14: Pyrazole synthesis from oxazoles

2.4.3 From Tetrazolo[1,5-a]pyrimidines, tetrazolo[1,5-a]pyridines, and tetrazolo[1,5-b]pyridazines are all types of tetrazoles. pyridazines are easily converted into cyanopyrazoles. At 140 °C, tetrazolyl acroleins and fumaronitrile react in xylene to produce the equivalent pyrazole formation, **Scheme of (15)** [15].



Scheme 15: Pyrazole from synthesis tetrazoles

3. PHARMACOLOGICAL ACTIVITY

3.1. Antibacterial

Several 1H-pyrazole-3-carboxylic acid derivatives' antibacterial properties against *Bacillus cereus*, Akbas et al. evaluated *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas putida*. (Figure 2). The findings demonstrated that the molecule, which exhibited Gram-positive and Gram-negative bacteria are both susceptible to antibiotic activity, was the best chemical in the series [16].

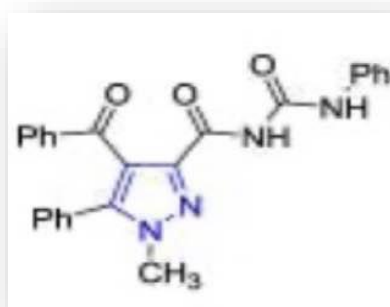


Figure 2: The chemical makeup of pyrazole derivatives as antibacterial agents

3.2. Anticancer Activity

It was discovered that a novel class of pyrazole-oxindoles (Figure 3) has antiproliferative effects on various cancerous human cell lines. Among the active ingredients shown notable cytotoxicity and an IC₅₀ that prevented tubulin assembly [17].

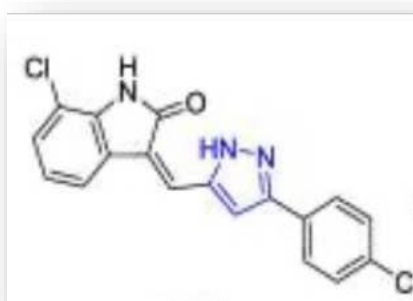


Figure 3: Structure of the anticancer pyrazole derivative

3.3 Anti-Inflammatory

A fresh class of pyrazole compounds was created (Figure 4) to be tested as selective COX-2 inhibitors. Results showed that the substance significantly inhibited COX-II (78.910.80%). [18]

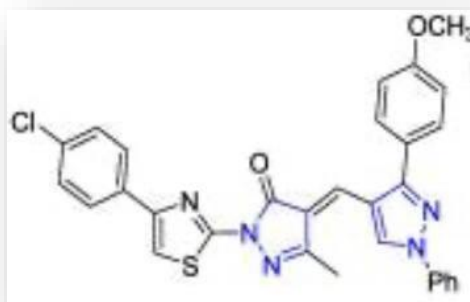


Figure 4: Pyrazolo-derived compound with anti-inflammatory properties

Effects of analgesics and anti-inflammatories of a number of 1-(4-substituted-phenyl)-3-phenyl-1H-pyrazole investigations were done on -4-carbaldehydes. The chemical that was produced showed the greatest inflammatory- and pain-relieving effects [19] (Figure 5). Tewari et al. created a brand-new class of pyrazole substances and was examined there in vivo anti-inflammatory efficacy. Exhibited equivalent among all substances, nimesulide has the best anti-inflammatory effectiveness. [20] (Figure 6).



Figure 5: Pyrazole derivative with painkilling and anti-inflammatory properties

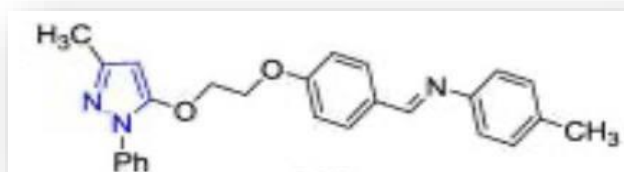


Figure 6: Pyrazole derivative with painkilling and anti-inflammatory properties

3.4 Anti-Tubercular Activity

In a sequence of 3-substituted 5-hydroxy-5-trifluoro [chloro] methyl-1H-1-isonicotinoyl-4, 5-dihydropyrazoles, Almeida da Silva et al. and examined there antimycobacterial efficacy in vitro against clinical isolates of Tuberculosis-causing mycobacterium that were INH-resistant and non-tuberculous mycobacteria. Compound was discovered to

be the most effective agent among the produced compounds against *M. tuberculosis* susceptible and several strains that are INH-resistant [21] (Figure 7).

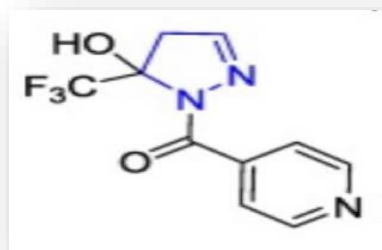


Figure 7: derivative of pyrazolo with antitubercular properties

3.5 Anti-Viral Activity

Manfredini et al. created a number of pyrazolo[4,3-d] and pyrazoleribonucleozides of 1,2,3-triazine-4-one (Figure 8) and examined their antiviral efficacy in vitro against HIV-1, polio, Coxsackie, the swine flu virus of Africa (ASFV), the vesicular stomatitis virus (VSV), and HSV-1. A substance displayed a preferential preventing HIV-1 replication among pyrazole nucleosides in C8166 cells with acute infection, [22].

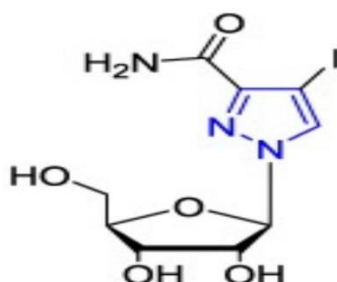


Figure 8: derivatives of pyrazole with antiviral properties

4. CONCLUSION

Many use of pyrazole derivatives for medical treatment is already common. Pyrazoles are an important pharmacophore with numerous biological characteristics. The literature review demonstrates the high pharmacological potency of pyrazole derivatives, indicating a prospective field of study in the design and production of these compounds. The basic structure of pyrazole has been structurally modified, allowing the creation with new derivatives a wide range of biological process. A majority significant structural changes so far have involved the substitutions the carbon at position 1, the replacement at position 3, and the carbon at position 5. According to earlier research, the fundamental molecule's structural modifications at various places enhance providing its pharmacological characteristics it antibacterial, Analgesic, anti-inflammatory, antiviral, and anticonvulsant properties, anti-cancer and anti-malarial qualities. The moment being, scientists are interested in creating more potent pyrazole compounds with a variety of biological activity.

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