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5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one: Synthesis and Reactions

[1]Khalid M. Darwish* and [2]Ahmed M. Ahmed

[1]Professor, Department of Chemistry, University of Benghazi, Libya - Benghazi

[2]BSc Graduate Student, Department of Chemistry, University of Benghazi, Libya - Benghazi

Corresponding author E-mail: kdarwish1962@gmail.com

REVIEW ARTICLE

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Abstract: The presence of the five-member pyrazole nucleus in different structures leads to a large diversity in its applications. In almost every research study, the pyrazole derivatives biological importance faces a competitive challenge in areas of technology, medicine and agriculture. This reflects the description of these derivatives as antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant as well as antiviral agents. In our review, we will discuss and show the highlights of chemical structure and tautomerism, the general methods of preparation of methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one as the core compound, including its synthesis from the β-Ketoesters and hydrazine derivatives and cyclization through hydrazone intermediates and the microwave-assisted and solvent-free synthesis. In addition, we will provide a close idea of derivatives of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one and present them as N-substituted and C-substituted derivatives, metal complexes as well as azo-dyes and chromophores. In the second part of this review, we will discuss the reactions of methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one such as the azo-coupling reactions, condensation reactions, alkylation, acylation and halogenation reactions, complex formation with metals in addition to the oxidation and reduction reactions. At the end of our review we will mention the applications and importance of this compound and its derivatives and their use across numerous scientific and industrial fields such as medicinal chemistry, dye and pigment synthesis, analytical chemistry assays, metal complexing agents, catalysts and sensors, synthetic intermediates, fluorescent materials, organic semiconductors and reactive monomers.

Keywords: Pyrazolones, Hydrazines, N-Substituted, C-Substituted, Alkylation, Azo dyes.

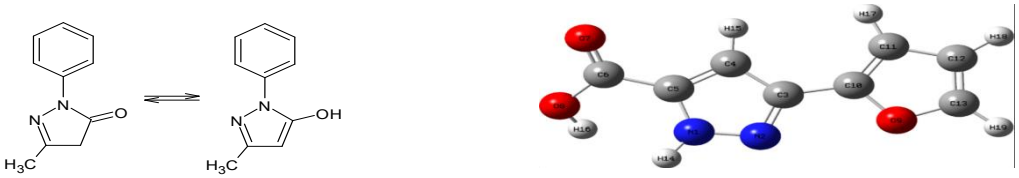
Introduction

5-Methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one is a heterocyclic organic compound belonging to the pyrazolone family, a class of five-membered nitrogen-containing heterocycles characterized by a 1,2-diazole ring fused with a carbonyl group. Pyrazolones are notable for their broad applications in synthetic organic chemistry, medicinal chemistry, dye chemistry, analytical chemistry, and coordination chemistry. Among them, 5-methyl-2-phenyl derivatives represent a highly versatile structural motif due to the presence of both electron-donating and electron-withdrawing substituents on the heterocyclic core, which significantly influence reactivity and pharmacologically relevant properties [1].

The compound exhibits a conjugated system involving the pyrazolone ring and a phenyl moiety, which contributes to characteristic stability and allows functional derivatization at multiple ring positions. Its molecular formula is commonly represented as $C_{10}H_{10}N_2O$, depending on tautomeric forms. The molecule can exist in several tautomeric states, most notably keto–enol tautomerism, which influences its behavior in solution, its ability to form metal complexes, and its participation in condensation reactions. The compound presents as a crystalline solid, typically pale yellow to white depending on purity, exhibiting characteristic UV absorption due to its benzene-pyrazolone conjugation [2].

Chemical Structure and Tautomerism

The structure of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one consists of a pyrazolone ring substituted by a phenyl group at the 2-position and a methyl group at the 5-position. The ring contains a carbonyl function at the 4-position and two adjacent nitrogen atoms at the 1 and 2 positions, giving rise to strong resonance stabilization. The tautomeric form of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one are shown in scheme 1.



Scheme 1. Tautomerism of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one

Ring positions
Position 1: nitrogen
Position 2: nitrogen substituted with phenyl
Position 3: CH
Position 4: carbonyl (C=O)
Position 5: substituted by methyl

A key chemical characteristic of pyrazolones is tautomerism [3]. The compound can adopt keto and enol forms, and in some media also exhibit lactam-lactim variations. The keto form typically predominates in the solid state, characterized by the presence

of a carbonyl at the 4-position. In polar solvents, hydrogen bonding can stabilize the enol form, where the carbonyl is partially reduced to an OH group while the adjacent ring positions rearrange electronic density. The tautomeric equilibrium influences IR spectra, NMR shifts, acidity, reactivity toward electrophiles and nucleophiles, and ability to form hydrogen. The aromatic phenyl ring at the 2-position introduces hydrophobicity and additional resonance pathways, enabling electrophilic aromatic substitution. The methyl group at the 5-position increases steric hindrance, modifies reactivity at the neighboring positions, and contributes to electron donation into the heterocycle. The presence of two nitrogen atoms with different electronic roles allows the compound to serve as a bidentate ligand in coordination chemistry, forming stable complexes with transition metals.

General Methods of Preparation

The synthesis of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one can be achieved through several classical and modern synthetic routes, depending on the desired efficiency, purity, and availability of precursor materials. Most preparations rely on condensation reactions involving β-dicarbonyl compounds and hydrazines, although multistep synthetic designs and catalytic modifications can also be employed.

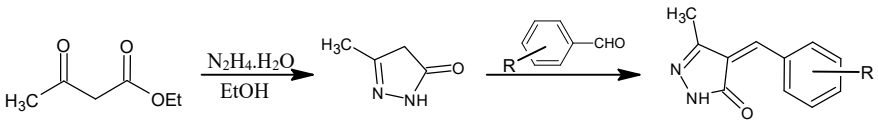
Below are the principal preparation strategies used in laboratory and industrial environments.

Synthesis from β-Ketoesters and Hydrazine Derivatives

A widely used method for synthesizing pyrazolones is the condensation of a β-ketoester with hydrazine or substituted hydrazine. For 5-methyl-2-phenyl derivatives, the typical precursor is ethyl acetoacetate, which introduces the 5-methyl group upon cyclization. Condensation involves nucleophilic attack of hydrazine on the carbonyl functionality, followed by cyclization and elimination of ethanol to yield the heterocycle.

To prepare a phenyl-substituted product at the 2-position, phenylhydrazine is used instead of unsubstituted hydrazine. The nucleophilic nitrogen of phenylhydrazine attacks the carbonyl carbon of ethyl acetoacetate, forming a hydrazone intermediate. Subsequent cyclization yields the characteristic pyrazolone ring.

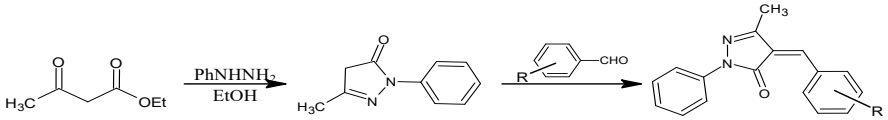
The reaction commonly occurs in ethanol, glacial acetic acid, or another protic solvent under reflux, and the product often crystallizes upon cooling. The reaction progresses efficiently and yields relatively pure pyrazolone, which can be further recrystallized from ethanol or a solvent mixture in Scheme 2 [4].



Scheme 2. Synthesis of pyrazolones from β-ketoester and different hydrazines

Cyclization Through Hydrazone Intermediates

Another method involves forming a hydrazone from phenylhydrazine and an acetoacetic ester or diketone, followed by intramolecular ring closure in Scheme 3. This method allows control over substituents at various ring positions and may give improved yields for specific derivatives [5].



R = H, OH (2,4), NO_2 (2,4), OCH_3 (2,3,4), $N(CH_3)_2$ (4), Cl (4)

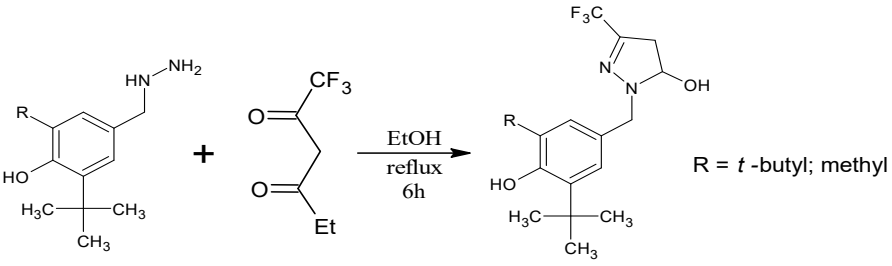
Scheme 3. Synthesis of pyrazolone from phenylhydrazine and an acetoacetic ester

The hydrazone intermediate typically undergoes ring closure upon heating, often facilitated by acid catalysts or Lewis acids. Cyclization proceeds via nucleophilic attack on the activated carbonyl group, followed by dehydration and aromatization. This controlled two-step process is favored for laboratories requiring high selectivity and reproducible yields.

Synthesis from β-Diketones

Using β-diketones, such as acetylacetone derivatives, yields pyrazolones upon condensation with phenylhydrazine. This reaction is particularly useful for constructing substituted pyrazolones with high carbonyl activation and increased reactivity. The resulting product often forms faster and requires milder conditions compared to β-ketoesters.

Reaction conditions can vary from room temperature to moderate heating. Protic or aprotic solvents may be used, and acidic catalysts often promote faster cyclization. The final product crystallizes readily and can be purified through standard washing or recrystallization procedures in Scheme 4.

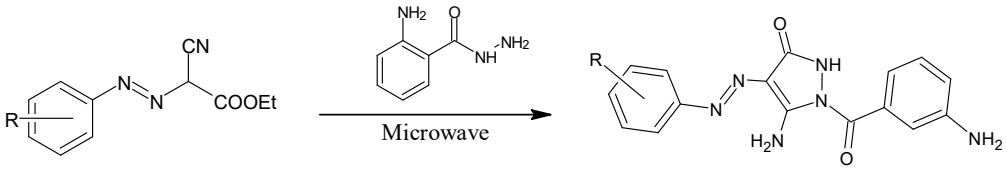


Scheme 4. Synthesis of pyrazolones from β-diketones

Microwave-Assisted and Solvent-Free Synthesis

Modern synthetic approaches favor environmentally friendly, solvent-free, or low-solvent conditions. Microwave irradiation dramatically reduces reaction time, often completing condensation and cyclization within minutes compared to hours under reflux.

Solvent-free grinding methods, using phenylhydrazine and diketones or ketoesters in the presence of a catalytic acid, have achieved good yields with minimal waste. These methods align with green chemistry principles, reduce purification burdens, and provide pyrazolone derivatives with excellent purity in Scheme 5 [6].

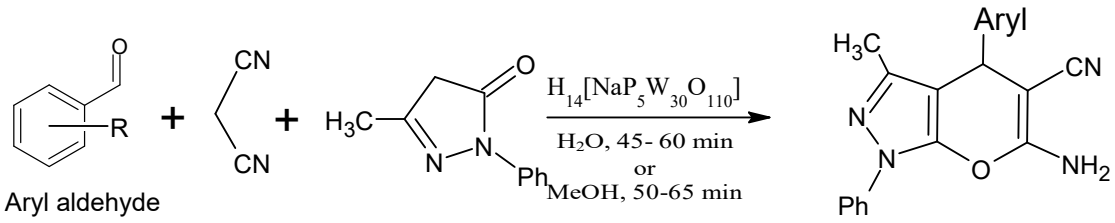


Scheme 5. Microwave-assisted synthesis of pyrazolone

Catalytic and Metal-Assisted Methods

Some reactions benefit from catalysts such as Lewis acids (e.g., $ZnCl_2$, $FeCl_3$, or $AlCl_3$), solid acid catalysts (e.g., silica-supported acids), or ionic liquids. These systems enhance electrophilic activation and may increase yields, especially for substituted variants.

Transition metal catalysts can direct regioselective formation, allowing tailored substitution at ring positions Scheme 6 [7].



Scheme 6. Acid catalyzed synthesis of dihydropyranopyrazole

Derivatives of 5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one

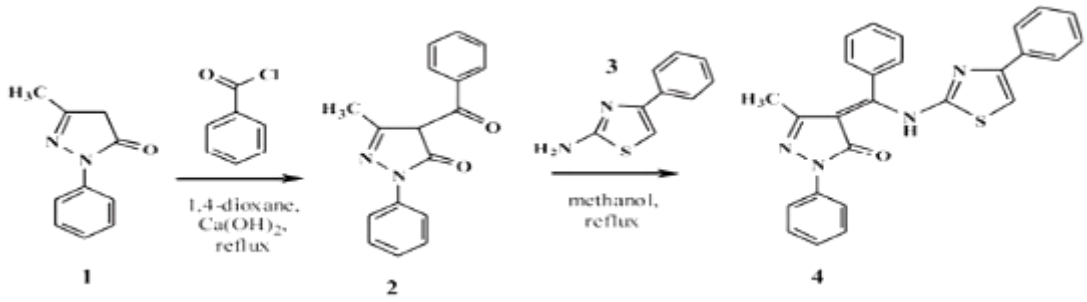
The pyrazolone structure is highly amenable to functional derivatization at multiple positions, allowing the formation of a broad library of chemical derivatives used in pharmaceuticals, dyes, analytical reagents, and coordination complexes.

Below is a detailed overview of common derivative categories.

N-Substituted Derivatives

Substitution at the N-1 position forms N-alkyl or N-aryl pyrazolone derivatives, accomplished through alkylation or acylation reactions. Reaction with alkyl halides, acyl chlorides, or sulfonyl halides yields N-modified products. These derivatives often show altered solubility, improved lipophilicity, and modified pharmacokinetic behavior in Scheme 7 [8].

N-aryl derivatives exhibit increased aromatic resonance coupling, influencing UV absorption profiles, making them useful in dye chemistry and analytical detection.

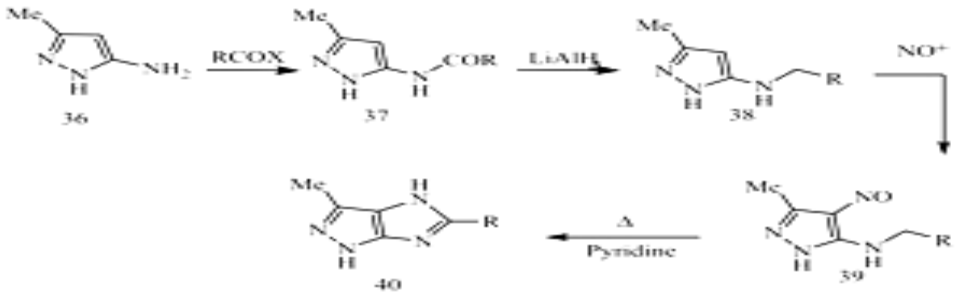


Scheme 7: Synthesis of N-substituted derivatives of pyrazolone

C-Substituted Derivatives

Carbon substitution commonly occurs at the 3-position or 4-position when the compound is converted into its enol tautomer. Electrophilic substitution at C-3 is facilitated by the adjacent electron-donating nitrogen atoms, while nucleophilic reactions at the carbonyl carbon are common at C-4.

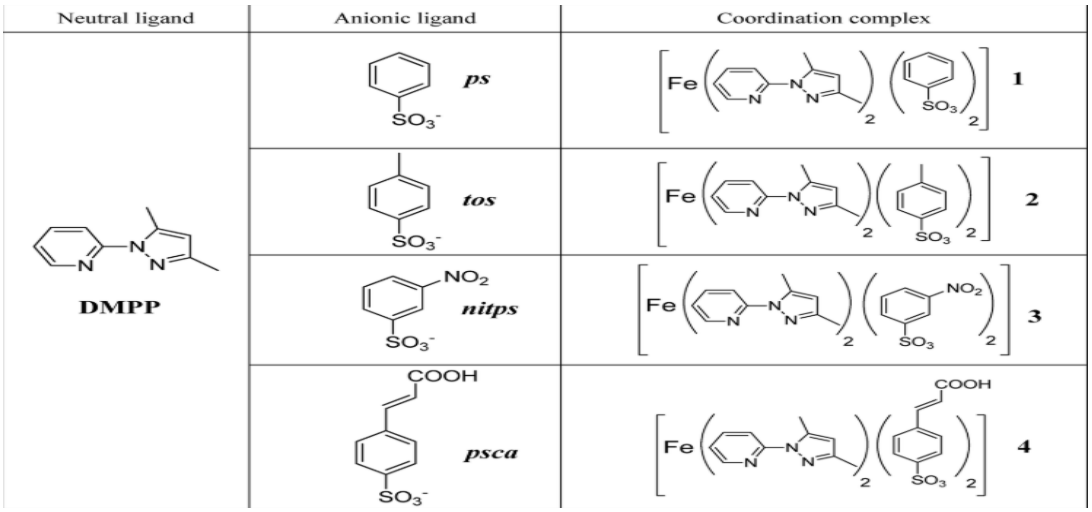
Typical substituents include halogens, nitro groups, carboxylates, and alkyl or aryl functionalities.
C-substitution improves biological activity, modifies acidity, and enhances metal-binding affinity in Scheme 8.



Scheme 8: Synthesis of C-Substituted derivatives of pyrazolone

Metal Complexes

Pyrazolones are known ligands in coordination chemistry due to their ability to bind metal ions via the carbonyl oxygen and ring nitrogen. Complexes of copper, nickel, cobalt, iron, zinc, and rare earth metals are well-studied.
These complexes exhibit distinctive magnetic, electronic, optical, and catalytic properties. They are used in analytical chemistry as colorimetric reagents, in catalysis, and in material science applications such as luminescent materials in Scheme 9 [9].

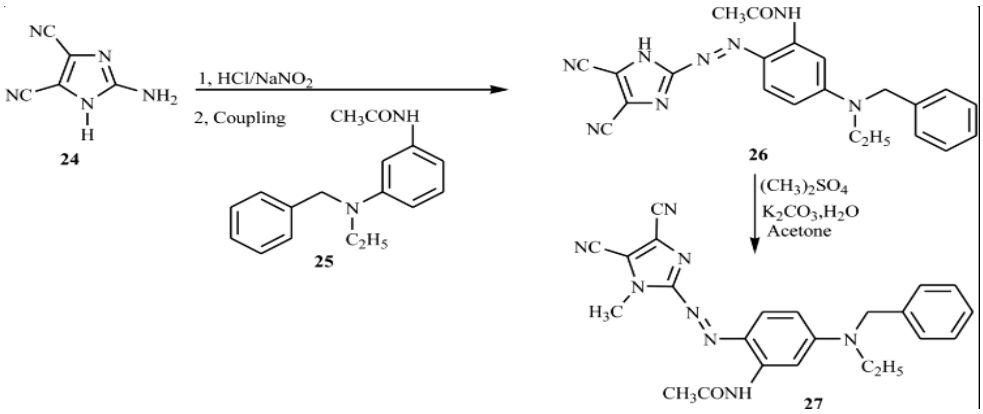


Scheme 9: Metal complexes of some pyrazolone derivatives

Azo Dyes and Chromophores

One of the most important derivative classes includes azo dyes formed by coupling the active methylene or enol form of pyrazolone with diazonium salts. The resulting azo dyes display vibrant coloration due to extended conjugation. These derivatives are widely used in textile dyes, pH indicators, analytical reagents, and sensor materials.

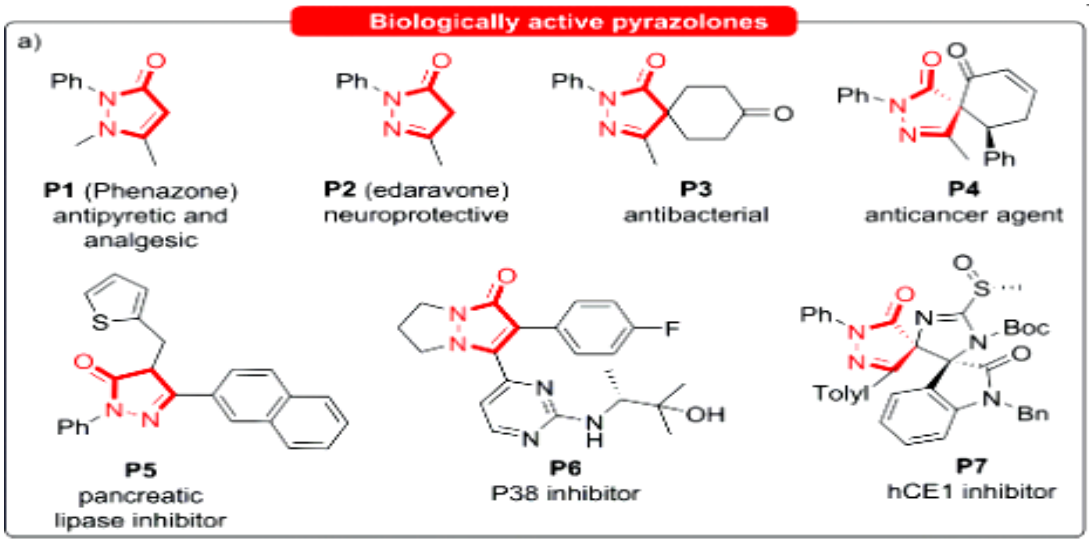
Phenyl-substituted pyrazolones provide enhanced chromophore stability, making them valuable as dye intermediates in Scheme 10 [10].



Scheme 10: Synthesis of azo dye from pyrazolone

Pharmaceutical Derivatives

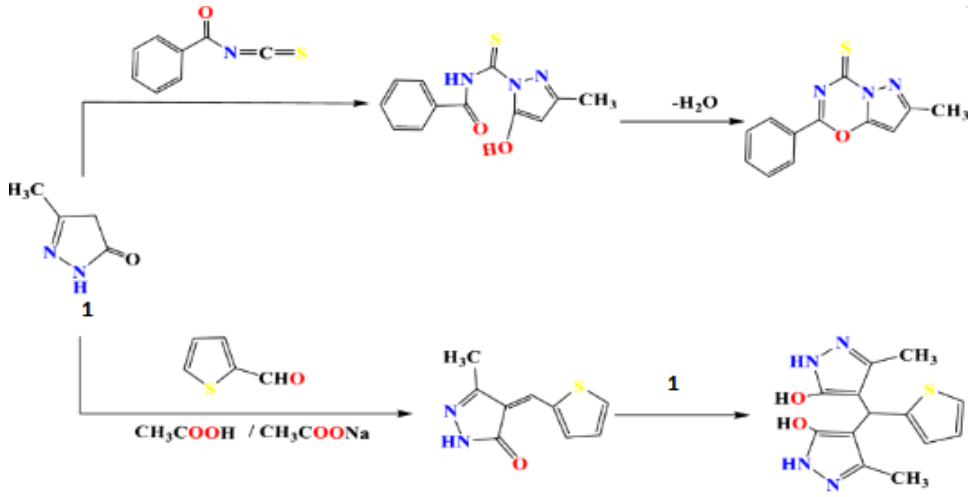
Pyrazolone derivatives historically contributed to analgesic, antipyretic, anti-inflammatory, and antimicrobial agents. Substituted pyrazolones can exhibit antioxidant, anticancer, and antiviral properties. The phenyl and methyl substituents provide structural aspects often required for lipophilicity and membrane permeability. Some derivatives act as enzyme inhibitors, metal chelators, or radical scavengers, making them useful in medicinal chemistry exploration in Scheme 11 [11].



Scheme 11: Pharmaceutical derivatives of pyrazolones

Reactions of 5-Methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-4-one

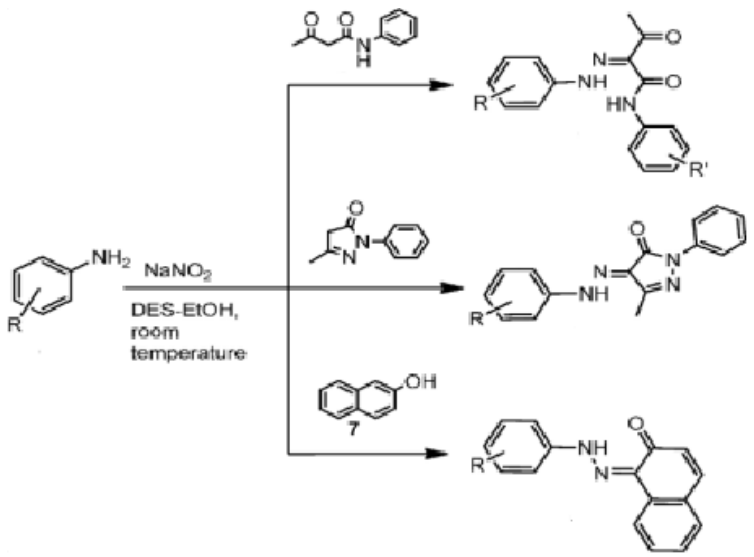
The compound participates in a wide range of organic reactions due to nucleophilic, electrophilic, and tautomeric features. Below is a detailed examination of its major reaction classes in Scheme 12.



Scheme 12: Reactions of pyrazolone with aromatic aldehydes and isothiocyanate

Azo Coupling Reactions

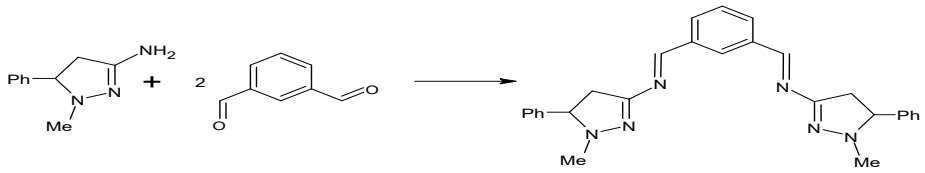
In its enolic form, the compound acts as a coupling component with diazonium salts to form azo dyes. Reaction typically occurs under mildly basic conditions, where the enol group undergoes electrophilic aromatic substitution with the diazonium reagent. Azo coupling produces intensely colored derivatives, often red, orange, or violet, depending on substituents. These reactions are crucial in analytical chemistry for spectrophotometric determinations and in industrial dye manufacturing in Scheme13 [12].



Scheme 13: Azo coupling reactions in pyrazolones

Condensation Reactions

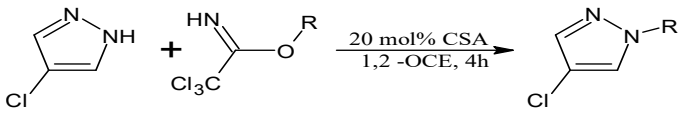
Pyrazolones having amino group can condense with aldehydes and ketones, forming Schiff base-type reactions at the enolic or amino positions. These reactions form extended conjugated systems and are useful in creating fluorescent dyes or biologically active molecules. Condensation with aromatic aldehydes forms styryl derivatives, while reaction with heterocyclic aldehydes produces hybrid systems with enhanced electronic effects in Scheme 14.



Scheme 14: Formation of Schiff's bases

Acylation and Alkylation

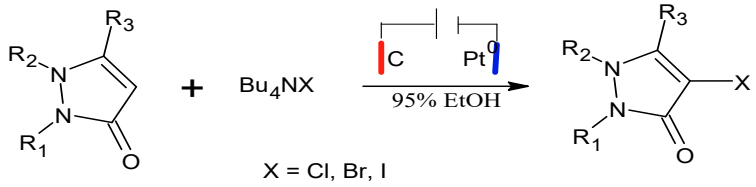
The nitrogen atoms and oxygen atom in the pyrazolone ring can undergo acylation with acid chlorides or anhydrides, yielding N-acyl or O-acyl products depending on tautomeric state.
Alkylation with alkyl halides yields N-alkylpyrazolones, altering pharmacological and physicochemical properties. These reactions require bases such as NaH, K_2CO_3, or tertiary amines in Scheme 15 [13].



Scheme 15: Acylation of pyrazolone

Electrochemical Oxidative Halogenation

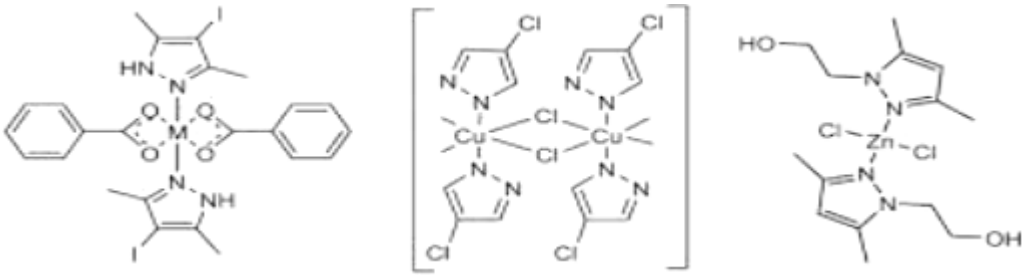
Electrophilic halogenation may occur at the active methylene position, especially when the compound adopts its enol form. Bromination or chlorination yields mono- or dihalogenated derivatives. These halogenated products serve as precursors for further nucleophilic substitution or cross-coupling reactions in Scheme 16 [14].



Scheme 16: Oxidative halogenation of pyrazolone

Complex Formation with Metals

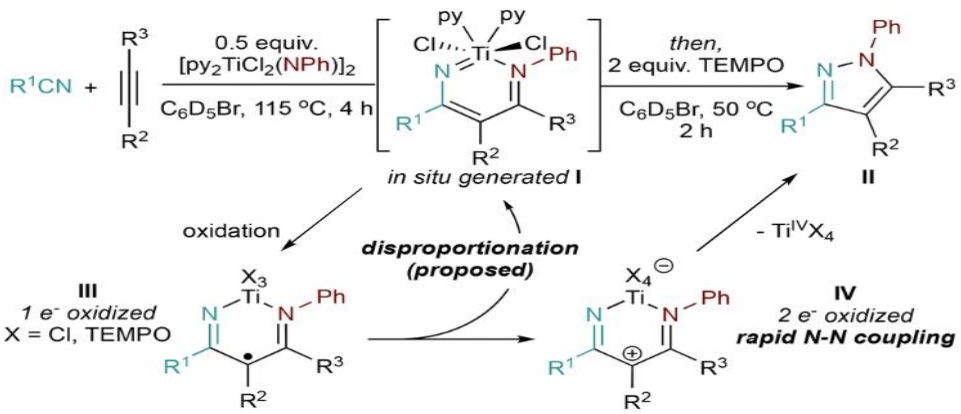
The carbonyl oxygen and ring nitrogen atoms coordinate with metal ions, forming stable chelates. The resulting complexes exhibit unique electronic transitions and magnetic signatures. Such reactions are important in materials chemistry, catalysis, and spectrophotometric metal determination in Scheme 17 [15].



Scheme 17: Complex formation

Oxidation and Reduction Reactions

Mild oxidation may convert the compound into dihydropyrazolones or modify the phenyl ring. Reduction can affect the carbonyl group or nitro-containing derivatives, depending on substituents. These reactions form important pathways in synthetic modifications and mechanistic studies in Scheme 18 [16].



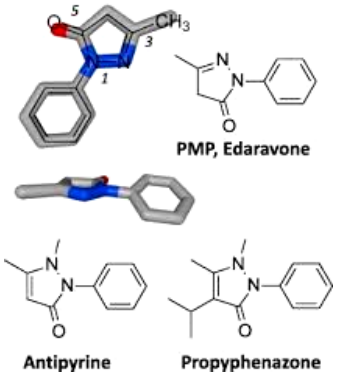
Scheme 18: Oxidation-Reduction reactions of Pyrazolone

Applications and Importance

The compound and its derivatives find use across numerous scientific and industrial fields:

Medicinal chemistry
Dye and pigment synthesis
Analytical chemistry assays
Metal complexing agents
Catalysts and sensors
Synthetic intermediates
Fluorescent materials
Organic semiconductors
Reactive monomers

The phenyl substitution provides extended conjugation, while the methyl group enhances structural stability and aromaticity of derivatives, making 5-methyl-2-phenyl pyrazolone highly adaptable.



Extended Overview of Spectroscopic Properties - Spectroscopic Information

The pyrazolone exhibits characteristic IR bands corresponding to carbonyl stretching near 1650 cm^{-1}, N–H stretching around 3200–3400 cm^{-1}, and phenyl ring vibrations in the 1500–1600 cm^{-1} region.
UV-Vis spectra show strong absorption due to the aromatic and heterocyclic conjugated system, typically around 240–300 nm.
^{1}H NMR spectra feature aromatic proton signals between 7.0–7.6 ppm, methyl proton signals around 2.2 ppm, and ring proton signals depending on tautomeric form.
Mass spectrometry reveals molecular ion peaks and characteristic fragmentation through loss of CH_3, phenyl, or CO moieties.

Conclusion

This comprehensive overview of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one (or antipyrine) outlines its structure, tautomerism, preparation, derivatives, reactions, and applications. The pyrazolone scaffold remains a cornerstone in heterocyclic chemistry due to its synthetic flexibility, rich reactivity, and broad utility across chemical and industrial domains. The compound's ability to undergo diverse transformations, form stable metal complexes, produce vivid azo dyes, and serve as a platform for bioactive derivatives establishes its continuing relevance in modern chemical research.
The presence of both phenyl and methyl substituents provides unique electronic, steric, and resonance characteristics that influence behavior in synthetic, biological, and physical contexts.

The compound stands as an important structural motif in medicinal chemistry, offering countless opportunities for drug design. Its rich reactivity enables formation of chromophores, advanced hybrid molecules, and functional materials. The versatility of its synthesis—from classical condensation routes to green, microwave-assisted methods—ensures accessibility for researchers.
Its derivatives continue to expand in scope, contributing to analytical chemistry through metal-binding reagents, to material science through coordination complexes, and to industry through dye production.

Through this detailed report, the compound's multifaceted nature becomes clear: 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-4-one remains a valuable heterocyclic cornerstone, shaping innovations across organic synthesis, pharmaceutical development, and chemical technology.

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