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SYNTHESIS AND EVALUATION OF PYRAZOLE DERIVATIVES BY USING GREEN CATALYST

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Green Synthesis and Characterization of 3,5-Dimethyl Pyrazole Derivative

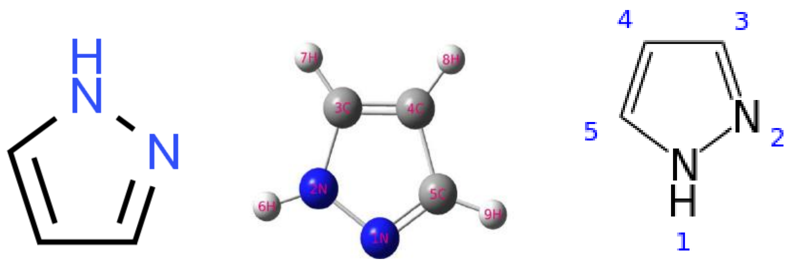
This study explores the sustainable synthesis of a pyrazole derivative, 3,5-dimethyl pyrazole, using a green catalyst, ammonium chloride. Knorr pyrazole synthesis was employed with ethanol as a renewable solvent, minimizing environmental impact. The synthesized product was characterized using various techniques, including melting point determination, Fourier-Transform Infrared (FTIR) spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, and evaluation of its antimicrobial activity. FTIR analysis confirmed the presence of functional groups, while NMR spectroscopy provided insights into the molecular structure. The antimicrobial activity assessment aimed to explore the potential of the synthesized compound against Staphylococcus aureus, a common pathogenic bacterium. The successful synthesis and characterization using green methods suggest that this approach holds promise for developing novel pyrazole derivatives with potential pharmaceutical applications.

Keywords: Pyrazole derivative, Green synthesis, Ammonium chloride, Knorr pyrazole synthesis, Antimicrobial activity, 3,5-dimethyl pyrazole, FTIR, NMR.

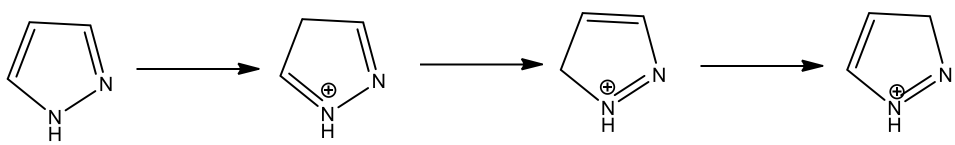
Introduction

- Pyrazole is a type of organic compound that has a heterocyclic ring
- consisting of three carbon atom and two adjacent nitrogen atom parallel to its structure.
- Pyrazole belongs to azole group having the chemical formula $C_3H_3N_2H$.
- The term pyrazole was first coined by Ludwig Knorr in 1883. They are known as alkaloids because of their structures and unique pharmacological effects on human beings
- The first natural pyrazole **1-pyrazolylalanine** was isolated from **watermelon seeds** in **1959.**
- The chemical reactivity of the pyrazole molecule can be explained by the action of each atom
- The N atom in 2nd position with two electron is a basic atom and therefore reacts with electrophiles
- The atom at 1st position dos not react but loses protons at present base.
- Two N atom combine to reduce the charge density at C3 and C5 making electrophilic attack possible.
- Many synthetic pyrazole compounds play an important role as colourant of drugs.
- Due to their good inhibitory activity derivative of pyrazole play an important role in in anticancer drugs.
- In addition, pyrazole derivative have good Anti-bacterial and Anti-inflammatory effects.
- Pyrazole and their derivative is also widely used as anti-tubercular, anti-fungal, anti-cancer, anti-viral, ACE inhibitor, anti-microbial, anti-convulsant, anti-inflammatory, neuroprotective.
- Pyrazole and their derivatives is used in agricultural activities as a insecticides and pesticides.

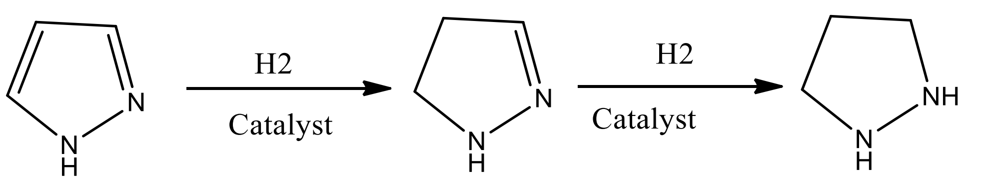
- **STRUCTURAL CHARACTERISTICS:**



- Pyrazole is a colourless solid with a melting point of 70°C.
- It is a tautomeric substance, Although tautomerism isn't appear in pyrazole itself, it can be inferred by its derivatives.
- Various resonating structures are possible for pyrazole.



- Pyrazole exhibits weak basic properties, enabling it to form salts with inorganic acids. It also allows for the replacement of the amino hydrogen with an acyl group.
- There are Some compounds which have stronger bases with pyrazole.



Pyrazole Pyrazoline Pyrazolidine

PHYSICAL AND CHEMICAL PROPERTIES:

Chemical formula	$C_3H_4N_2$
Molar mass	68.079 g·mol^{-1}
Melting point	66 to 70 °C
Boiling point	186 to 188 °C
Basicity (pK_b)	11.5

Introduction to Green Chemistry

Green chemistry is an innovative field within chemistry that aims to design chemical products and processes that minimize or eliminate the use and production of harmful substances. Essentially, it focuses on making chemistry more sustainable.

Traditionally, the field of chemistry has prioritized the creation of new and beneficial products, often without considering environmental impacts. Green chemistry adopts a more comprehensive perspective, evaluating the entire life cycle of a chemical product—from design and production to usage and disposal.

Key objectives of green chemistry include:

- Minimizing or eliminating hazardous substances: This involves reducing the use of toxic chemicals, solvents, and catalysts.
- Designing safer products: Creating products that are biodegradable or easily recyclable.
- Reducing waste: Aiming to prevent waste generation from the outset rather than addressing it post-production.
- Using renewable resources: Favoring the use of renewable resources like biomass.
- Designing energy-efficient processes: Developing chemical processes that require less energy.

Green chemistry has the potential to transform various industries, such as:

- Pharmaceuticals
- Materials science
- Agriculture
- Energy production
- Consumer productsBy fostering more sustainable chemical processes, green chemistry can help protect our environment and promote a healthier future for coming generations.

The 12 Principles of Green Chemistry provide guidelines for creating more sustainable products and processes:

1. Prevent waste: Prioritize waste prevention over cleanup.
2. Atom economy: Ensure maximum incorporation of materials into the final product.
3. Less hazardous chemical syntheses: Use and produce substances with minimal toxicity.
4. Safer solvents and auxiliaries: Opt for safe, environmentally friendly solvents and auxiliaries.
5. Design for safety: Create products that are inherently safer for health and the environment.
6. Design for energy efficiency: Reduce the energy needed for chemical processes.
7. Use of renewable feedstocks: Prefer renewable resources whenever possible.
8. Reduce unnecessary derivatization: Avoid unnecessary chemical modifications.
9. Catalysis: Employ catalytic reagents to minimize waste.
10. Design for degradation: Ensure products break down into harmless substances post-use.
11. Analyze for pollution prevention: Incorporate environmental impacts into life cycle analysis.
12. Safe chemistry for accident prevention: Develop safer chemicals to reduce the risk of accidents.

LITERATURE SURVEY

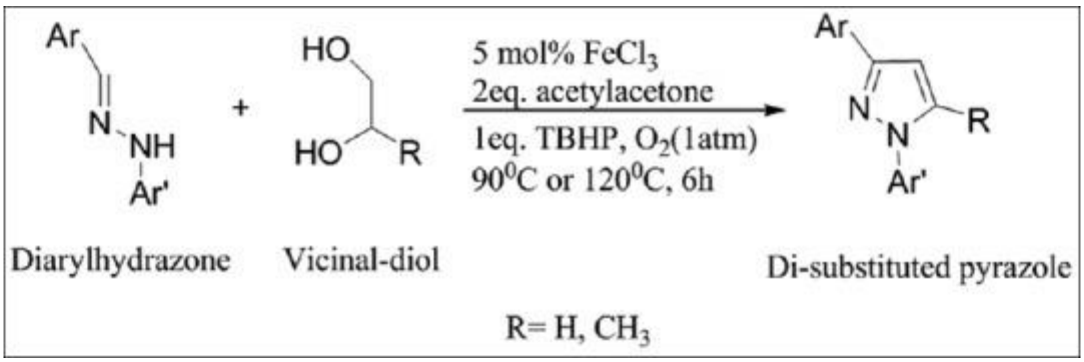
VARIOUS SYNTHESIS METHOD OF PYRAZOLE:

- The term pyrazole was given to this class of compounds by German Chemist **"LUDWIG KNORR"** in 1883.
- This was the first discovery of pyrazole derivative used as medicinal agent, it stimulated the interest in pyrazole chemistry.
- There are many synthetic methods have been developed for the preparation of pyrazole derivatives. In general, pyrazoles are synthesized by the reaction of

(i) 1,3-Diketones with hydrazines.
(ii)α,β-Unsaturated aldehydes and ketones reaction with different hydrazine.
(iii) Vilsmeier-Haack reaction of hydrazones

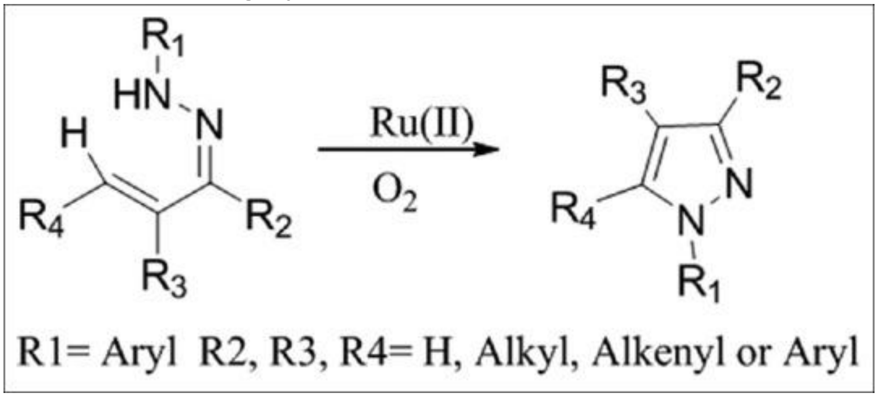
1. Synthesis of 1, 3-substituted pyrazoles

An iron-catalyzed route for the regioselective synthesis of 1,3- and 1,3,5-substituted pyrazoles from the reaction of diarylhydrazones and vicinal diols.



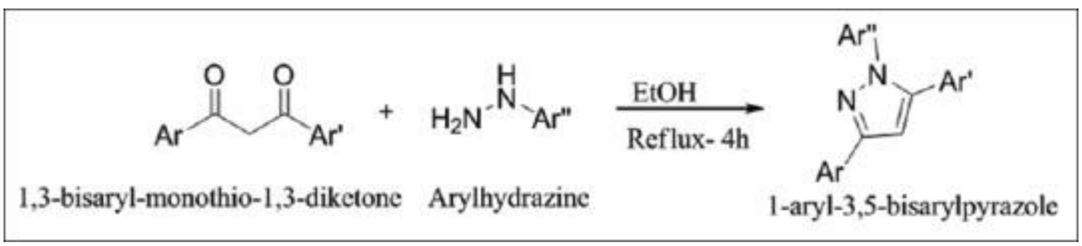
2. Synthesis of tri- and tetra-substituted pyrazoles:
A ruthenium (II)-catalyzed intramolecular oxidative CN coupling method for the facile synthesis

of a tri- and tetra-substituted pyrazoles. Dioxygen gas is employed as the oxidant in this transformation and the reaction demonstrates excellent reactivity, functional group tolerance, and high yields.

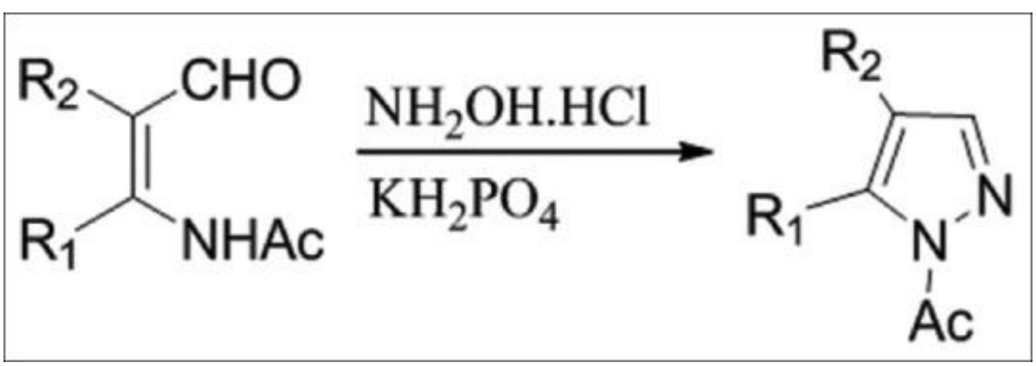


3. Synthesis of 1,3,5-trisubstituted-1H-pyrazole

The reaction of the easily accessible 1, 3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-propenones with arylhydrazines gives 1-aryl-3,5-bisarylpyrazoles with complementary regioselectivity at position 3 and 5.



4. Synthesis of 1-(4,5-disubstitutedpyrazol-1-yl)-ethanone.
A novel one-pot synthesis of pyrazoles has been accomplished by the reaction of β-formyl enamides with hydroxylamine hydrochloride catalyzed by potassium dihydrogen phosphate in acidic medium.



AIM OF PROJECT:

To Synthesize pyrazole Derivatives By Using Green Catalyst.

OBJECTIVES:

Synthesis, purification, characterization of new synthesized molecules of coumarin derivatives by spectral analysis such as IR,1H NMR and elemental analysis.

Screening of the new molecules for their biological activities such as antimicrobial.

Let's protect our environment by choosing better materials and figuring out new ways to change them. This means creating processe that are safer and less likely to release harmful chemicals, catch fire, or explode.

Plan of work

Literature Survey

↓

Material and methods

↓

Experimental work

↓

Preparation of pyrazole derivative

↓

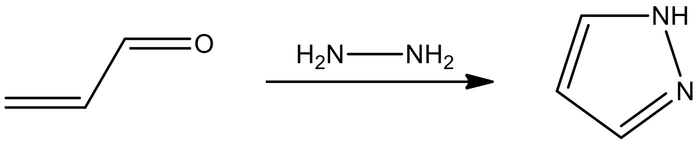
Result and discussion

MATERIALS AND METHOD:

- Sustainability is at the forefront of scientific advancements. In line with this trend, wepresent a method for synthesis of pyrazole derivatives that eliminates solvents andutilizes a cost-effective, environmentally benign catalyst.
- Here we synthesized pyrazole derivatives from knorr pyrazole synthesis inpresence of green catalyst as ammonium chloride.
- All chemicals employed in this research were sourced from Vishal Chemicals,Bhiwandi, India.

GENERAL SYNTHESIS OF PYRAZOLE:

Acetyl acetone and hydrazine hydrate gives 3,5-dimethylpyrazole



In knorr pyrazole synthesis hydrazine and 1,3- dicarbonyl compound converted into pyrazoles with the help of catalytic acid.

The acid is deprotonated by the dicarbonyl and is subsequently attacked by the hydrazine to produce an amine.

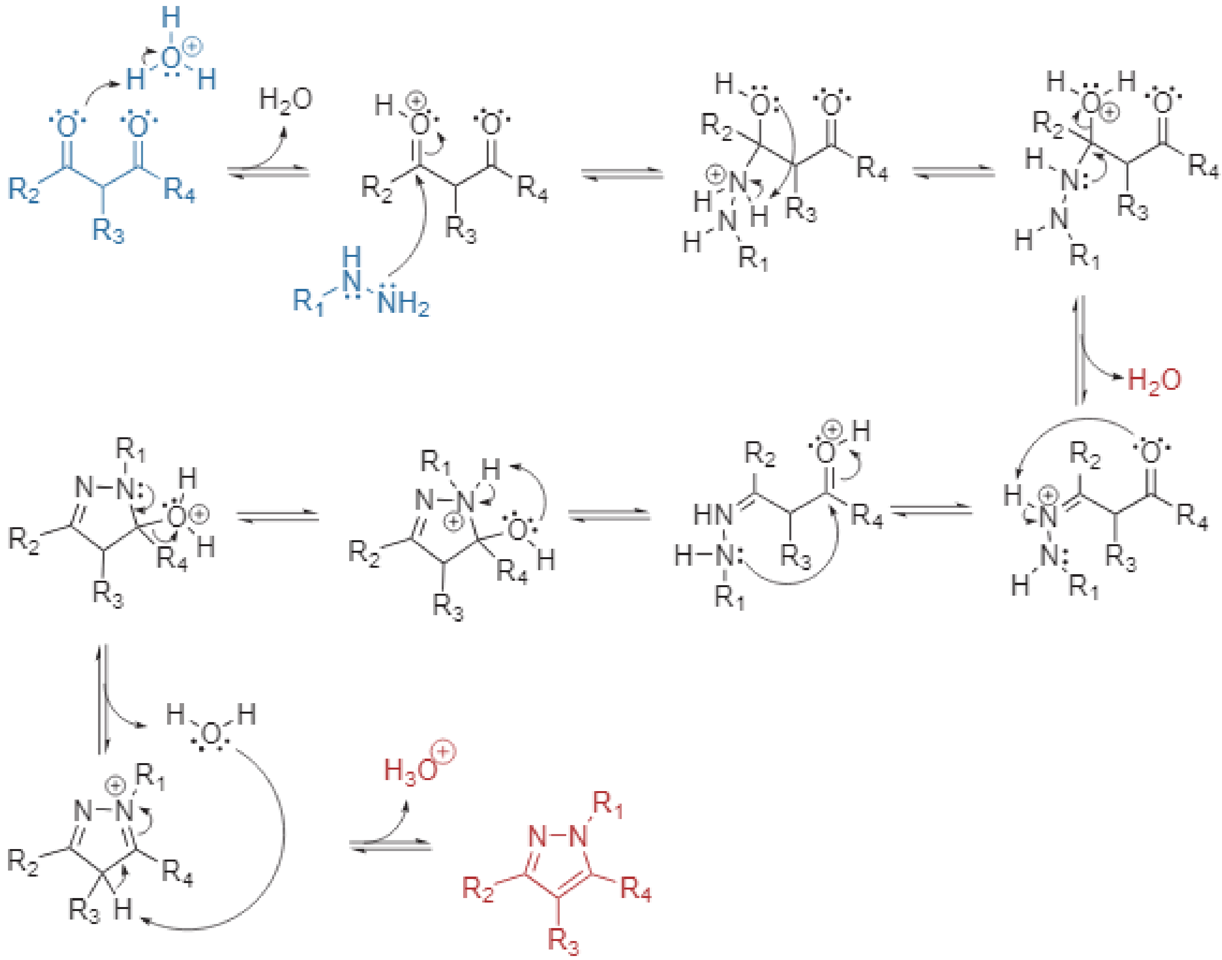
For the formation of second amine the second nitrogen of hydrazine will attack the second carbonyl group.

Then diamine is deprotonated to recreate the catalyst which results in the final pyrazole products.

Claisen Condensation-Hydrazinolysis:

This approach involves a two-step process: first, a Claisen condensation between an ester and a ketone to form a β-diketone, followed by hydrazinolysis with hydrazine to cyclize the pyrazole ring

Mechanism:



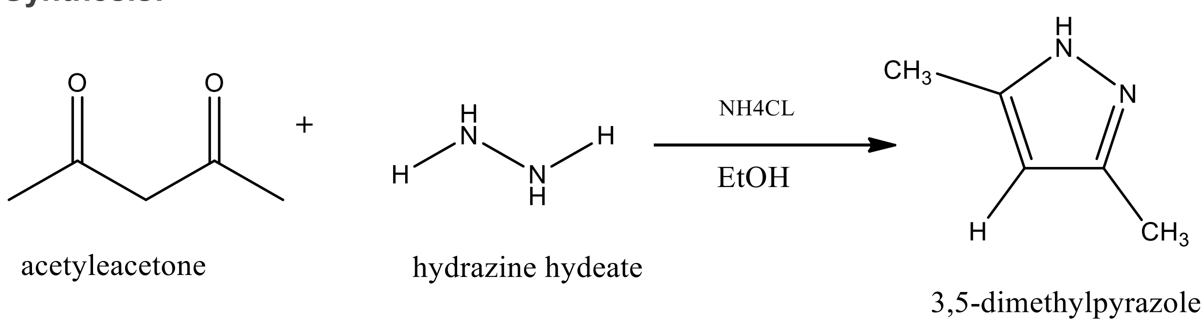
SYNTHESIS OF 3,5-DIMETHYL PYRAZOLE FROM AMMONIUM CHLORIDE AS A GREEN CATALYST .

Ammonium chloride is a readily available, inexpensive, and non-toxic catalyst. Ethanol is a renewable solvent compared to traditional organic solvents. Water is used for work-up and crystallization, minimizing waste.
The procedure allowing for easier isolation and purification of the product.

Ammonium chloride is white crystalline solid having the following physical properties:

Molecular formula	NH4Cl
Molar weight	53.49 g/mole
Odor	odorless
Melting point	338 °C (decomposes)
Boiling point	520 oC
pH	5.5 (acidic)
Density	1.5274 g/cm3

Synthesis:



Procedure;

- In a dry round-bottom flask, dissolve 20 mmol of the acetyl acetone in 100 mL of ethanol.
- Add 40 mmol of hydrazine hydrate and 2 mmol of ammonium chloride.
- Optionally, add a few drops of glacial acetic acid as an additional catalyst.
- Stir the mixture thoroughly using a magnetic stirrer around 30-45 minutes to stir well.

Reflux:

- Attach the condenser to the round-bottom flask.
- Heat the mixture under reflux conditions using a heating mantle for 4-6 hours.
- After heating remove the solution from the round bottom flask.

Work-up:

- Allow the reaction mixture to cool down to room temperature.
- Filter the mixture through a Buchner funnel fitted with filter paper to remove the ammonium chloride precipitate.
- Concentrate the filtrate using a rotary evaporator under reduced pressure.

- Add distilled water to the residue and stir to dissolve any remaining salts.

Crystallization:

- Slowly add the aqueous solution to a beaker containing chilled water.
- The pyrazole product should crystallize out.
- Filter the crystals and wash with cold water.
- Recrystallize the product from a suitable solvent from methanol to obtain pyrazole.

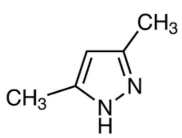
RESULT AND DISCUSSION:

- Synthesis of 3,5-dimethyl pyrazole a derivative of pyrazole obtained from knorr pyrazole synthesis using ammonium chloride as a green catalyst.
- FTIR Spectrum was used to identify the functional group of the active compounds present in sample based on the peak value in the region of infrared radiation.
- Nuclear magnetic resonance is a technique of an analytical chemistry which used in quality control and research for determining the content and purity of sample as well as its molecular structur

IR OF PYRAZOLE DERIVATIVE

3,5- DIMETHYL PYRAZOLE

STRUCTURE:



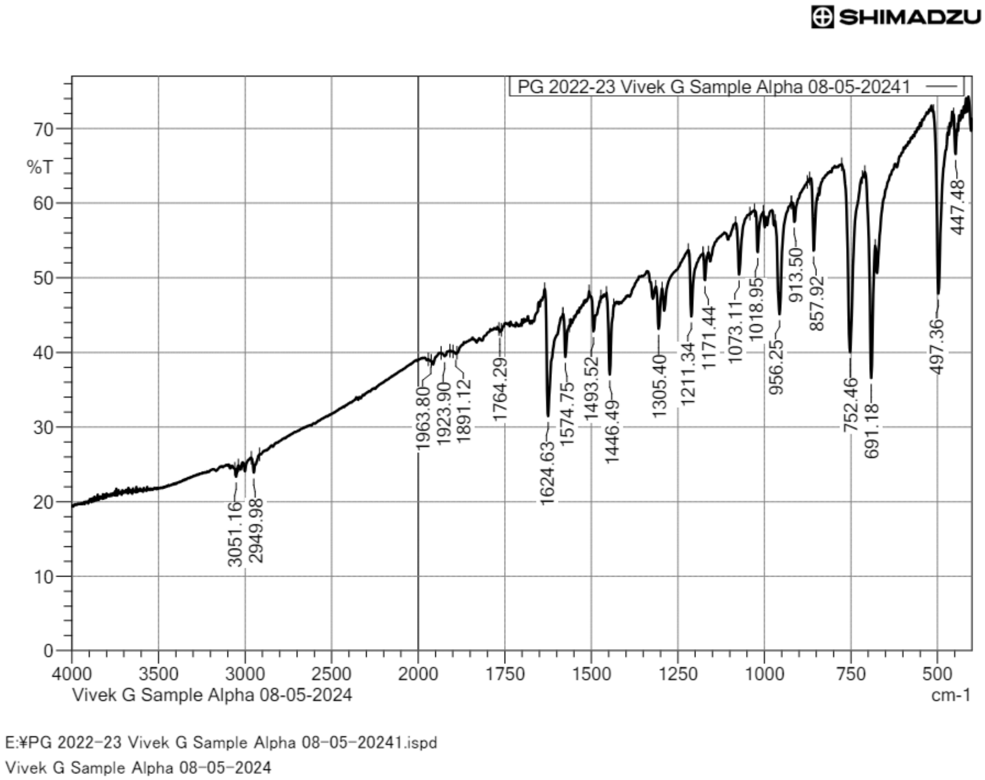
IR STUDY:

Wavenumber around 3051.16 cm-1: This peak is O-H stretching in an alcohol or carboxylic acid.

Wavenumber around 2949.98 cm-1: This peak is due to C-H stretching in alkanes.

Wavenumber around 1764.29 cm-1: This peak is due to C=O stretching in a ketone or aldehyde.

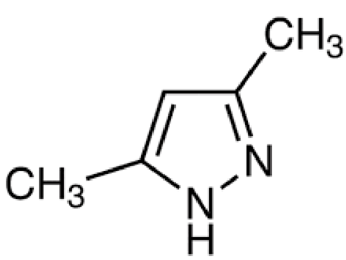
Wavenumber around 1624.63 cm-1: This peak is due to C=C 1490.93 cm-1: This peak is due to N-H bending in a primary amine.



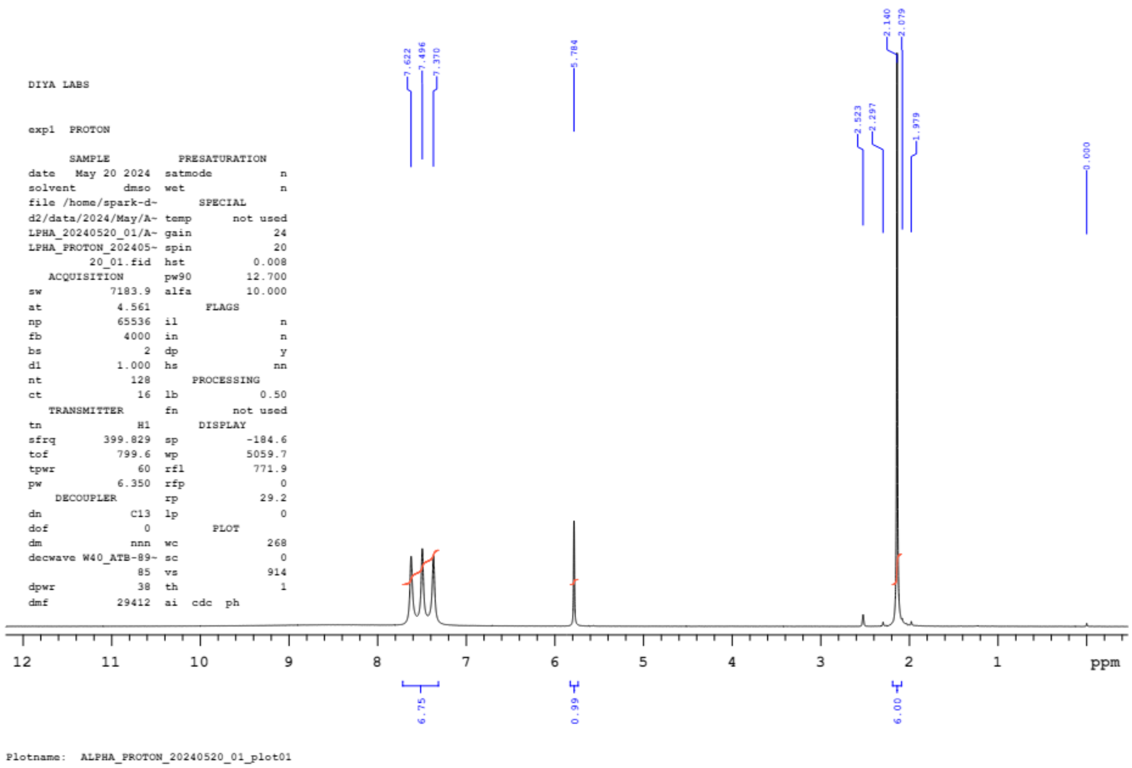
NMR OF PYRAZOLE DERIVATIVE:

3,5- DIMETHYL PYRAZOLE

STRUCTURE:



NMR STUDY:


DIYA LABS
exp1 PROTON
SAMPLE PRESATURATION
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LPHA_20240520_01/A~ gain 24
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20_01.fid hst 0.008
ACQUISITION pw90 12.700
sw 7183.9 alfa 10.000
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np 65536 il n
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d1 1.000 hs nn
nt 128 PROCESSING
ct 16 lb 0.50
TRANSMITTER fn not used
tn H1 DISPLAY
sfrq 399.829 sp -184.6
tof 799.6 wp 5059.7
tpwr 60 rfl 771.9
pw 6.350 rfp 0
DECOUPLER rp 29.2
dn C13 lp 0
dof 0 PLOT
dm nnn wc 268
decwave W40_ATB-89~ sc 0
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dpwr 38 th 1
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7.622 7.496 7.370 5.784 2.523 2.297 2.140 2.079 1.979 0.000
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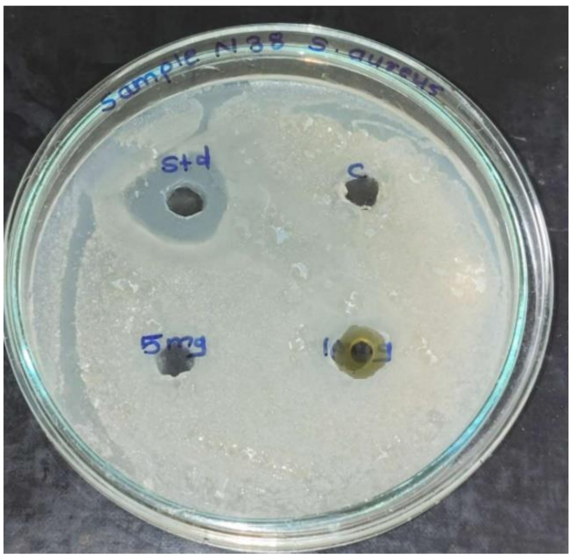
6.75 0.99 6.00
Plotname: ALPHA_PROTON_20240520_01_plot01

ANTI-MICROBIAL ACTIVITY OF PYRAZOLE DERIVATIVE:

Observations:

Dose of compound: 5 mg/ml Control : DMSO 10 mg/ml Dose of standard:1 mg /ml

Sr No. sample	Concentration	Zone of inhibition(mm) S. aureus
1 Control	-	-
2 Standard drug streptomycin	1mg/ml	24
3 Sample N1	5 mg/ml	Nil
	10mg/ml	15



Staphylococcus aureus Slant ATCC no.6538

CONCLUSION:

During this study, it has been found that sample showed inhibiting the growth of micro- organisms against S.aureus

ANTI-MICROBIAL ACTIVITY:

- Pyrazole and their derivatives has various anti-microbial and antibacterial activity they target bacteria and inhibit them from growth.
- Microbial diseases such as diphtheria, plague, cholera, pneumonia typhoid & tuberculosis have taken high toll of humanity in recent pasts.

- Now a days , many of the antimicrobial drugs are toxic and create recurrence of diseases because they are bacteriostatic and not bacteriocides.

- *S. aureus* is one of the most common types of microbes that approx. 30% of populationcarry in their noses, and 2% of population carries methicillin-resistant *S. aureus*(MRSA) drug-resistant variant, which causes the highest number of invasive infection among all the antibiotic-resistant bacteria.

- variety of serious and fatal pathologies cause by *S. aureus* including, endocarditis, pneumonia, osteomyelitis, skin infections and sepsis.

CONCLUSION:

3,5-dimethyl pyrazole a derivative of pyrazole is prepared from knorr pyrazole synthesis from green catalyst ammonium chloride as green catalyst and it is confirmed by the Melting point, IR spectrum, NMR spectroscopy and Microbial testing.

APPLICATION

Pharmaceuticals: This is the most prominent application area for pyrazole derivatives. They exhibit a wide range of biological activities, making them valuable drug candidates:

- **Pain relief and inflammation:** Celecoxib, a blockbuster drug, belongs to this category.
- It acts as a COX-2 inhibitor, effectively managing pain and inflammation. Other examples include phenylbutazone and nimesulide.
- **Sleep aids:** Zaleplon, a sleep medication, is a pyrazole derivative that promotes sleep by enhancing the action of a specific neurotransmitter.
- **Anticonvulsants:** Some pyrazole derivatives possess anticonvulsant properties, meaning they help control seizures. Examples include firomepizole and loreclezole.
- **Antidepressants:** Researchers are actively exploring the potential of pyrazoles in treating depression due to their effects on neurotransmitters.
- **Antifungal agents:** Certain pyrazole derivatives exhibit antifungal activity, making them valuable in combating fungal infections. Examples include difenoconazole and epoxiconazole.
- **Other therapeutic areas:** Pyrazole derivatives are also being investigated for their potential in treating various other conditions, including cancer, tuberculosis, and allergies.

Agrochemicals: Pyrazoles play a crucial role in agriculture:

- **Insecticides:** Fipronil, a widely used insecticide, belongs to the pyrazole class. It effectively controls a broad spectrum of insects that harm crops.
- **Fungicides:** As mentioned earlier, some pyrazole derivatives possess antifungal properties, protecting crops from fungal diseases. Examples include metconazole and tebuconazole.
- **Herbicides:** A limited number of pyrazole derivatives act as herbicides, controlling unwanted weeds in crop fields.

Materials Science: Pyrazoles find applications in material science due to their unique properties:

- **Fluorescent dyes and labels:** Pyrazole derivatives can be designed to exhibit fluorescence,

making them valuable in various applications, such as biological staining and sensor development.

- **Corrosion inhibitors:** Some pyrazole derivatives can inhibit corrosion in metals, protecting them from degradation.

Other Applications: Pyrazoles have additional applications in various fields:

- **Food additives:** Certain pyrazole derivatives are approved for use as food additives, such as flavoring agents or preservatives.
- **Catalysis:** Pyrazoles can be used as ligands in catalysts, improving the efficiency of chemical reactions.

Future Potential: Research on pyrazoles and their derivatives is ongoing, with scientists exploring their potential in various new applications, including:

- **Development of more targeted and effective drugs with fewer side effects**
- **Creation of novel agrochemicals with improved environmental profiles**
- **Discovery of new functional materials with specific properties**

The diverse properties and ongoing research make pyrazole derivatives a promising class of compounds with significant potential to impact various fields in the future.

Summary

Our work is based on synthesis of pyrazole der under solvent free condition using green catalyst

Here we synthesized 3,5-dimethyl pyrazole a derivative by knorr pyrazole synthesis using green catalyst

Instead of harmful catalyst harmful catalyst.

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