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Review Article

Advances in Pyrazole Ring Formation and Their Methodologies: Review

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ABSTRACT

The purpose of this review was to discuss the pyrazole synthesis method. The significance of significant groups of heterocyclic compounds that generate pyrazoles has only increased due to their broad range of biological activity-based research areas. The biological functions of pyrazole are diverse. These compounds are employed in pharmacological research and the creation of agricultural goods. The aim of this review is to offer a comprehensive overview of the published research related to the synthesis of pyrazole derivatives, encompassing a discussion of diverse methods for accessing the pyrazole moiety, The technique created for synthesis of pyrazole are therefore becoming increasingly significant.

INTRODUCTION

Pyrazole, a five-membered heterocycle containing two nitrogen atoms[1] ,More over half of all known chemical compounds are heterocycles, which are important types of molecules. several drugs, the majority of supplements, several natural products, and biomolecules such as hormones, antibiotics, alkaloids, vitamins, and so forth include them.[2]In fact, pyrazoles are a broad family of heterocycles that may be investigated for the creation of novel pharmaceutical compounds.[3]The simplest member of pyrazole family is pyrazole itself, a compound with molecular formulae C3H4N2[4]. 1,2,4-triazoles have been well documented[5].Heterocyclic structural elements are included in the great majority of synthetic medications that are sold commercially[2]. they are found in a large number of drugs and naturally occurring molecules with antifungal[6], antiparasitic, antimicrobial, anti-inflammatory, anticancer, antihypertensive , analgesic[7], antiviral, and antidiabetic activity just a few of the many heterocyclic compounds that have been shown to a have broad range of biological properties.[8] Pyrazoles are highly versatile and find applications in various industries including chemicals, pharmaceuticals, medications, and agriculture[9], polymer

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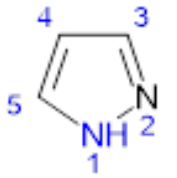
chemistry.[10] One kind of heterocyclic chemical is pyrazole. First, pyrazole was produced in Figure 1 by decarboxylating pyrazol-3,4,5-tricarboxylic acid.[11]



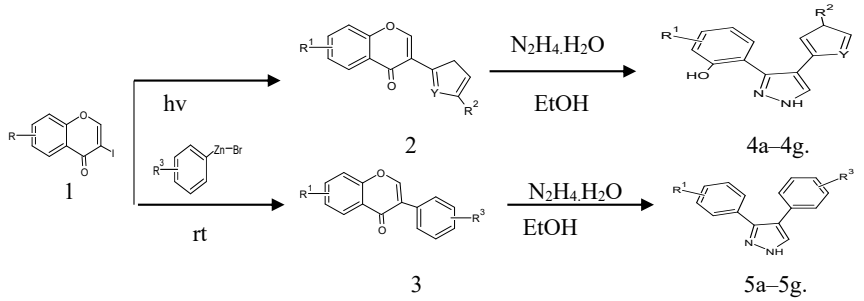
Pyrazole

Pyrazole was thought to be non-existent from nature until recently. However, a Japanese plant belonging to the Tropical Asiatic "Piperaceae" family identified the first naturally occurring pyrazole derivative. We extracted pyrazolic amino acids from watermelon seeds (Citrullus vulgaris). [11] Ludwig Knorr originally used the term "pyrazole" in 1883[12]. Due to their widespread presence in natural products, nitrogen-containing heterocycles are among the most active substances. Numerous applications in biology, chemistry, and other disciplines are also demonstrated by them. Furthermore, heterocycles containing nitrogen are important in coordination chemistry[2]. The five-membered heterocycle 1H-pyrazole, on the other hand, belongs to a family of substances that have drawn a lot of interest because of its synthesis and efficient significance for biology[13]. Many physiologically significant natural compounds and alkaloids, including serotonin, vitamin B1, morphine, atropine, coniine, nicotine, caffeine, and different NSAIDs, include subunits of these cores[14]. In our earlier study, 3,4-diaryl-1H-pyrazoles derivatives were produced and their antioxidant properties were evaluated. These compounds showed antibodies to heat-shock protein 70 and anticancer[15]. Hydrazine derivatives of 1,3-diketones. The synthesis of pyrazole derivatives using the pyrazole as the central core is the focus of another method. Our goal is to examine the processes involved in the synthesis of several additional substituted and condensed pyrazoles, namely the potential of 5 chloro- and 5-azido-1,3-diphenyl-1H pyrazole-4-carbaldehydes[16]. The carbostyril (2-quinolone) ring system is a significant family of chemicals due to its antibacterial properties as well as its theoretical relevance[17]. Produce a unique 5-substituted phenyl pyrazole with a heterocyclic ring to produce some intriguing new anti-inflammatory drugs[18]. 3,5-Diaryl Pyrazole is chemically synthesized from α, β unsaturated ketones using a carbonyl chromophore on the N-1 position. Thus, the purpose of this research is to create 3,5-diaryl derivation of pyrazole from the precursor chalcone[19]. Recent years, our group have reported a number of novel pyrazole derivatives. Many FDA-approved and commercially accessible medications, both patented and non-patented, have been made with pyrazole derivatives in recent years. The widespread use of these groups in the synthesis of new bioactive chemicals is highlighted by this trend. This evaluation explains pyrazole pharmacophore synthesis in brief, making it a useful reference manual for researchers working on this area. Chemical synthesis categories are used to roughly categorize the perspective[20]. Numerous pyrazole compounds, both natural and synthetic, have a broad range of pharmacological potentials and druggable qualities[21]. In this work, we would like to present some pyrazole derivatives that meet these structural specifications[22].

Methods:

2.1 Synthesis of 3-phenyl-4-heteroaryl-1H-pyrazoles and 3,4-diphenyl-1H-pyrazoles : Zun-Ting Zhang et.al aim to performed Hydrazine hydrate (2 mmol) and compound 3-Heteroarylchromones or 3-Phenylchromones (1 mmol) were refluxed in ethanol (15 mL) for approximately two hours. TLC tracked every

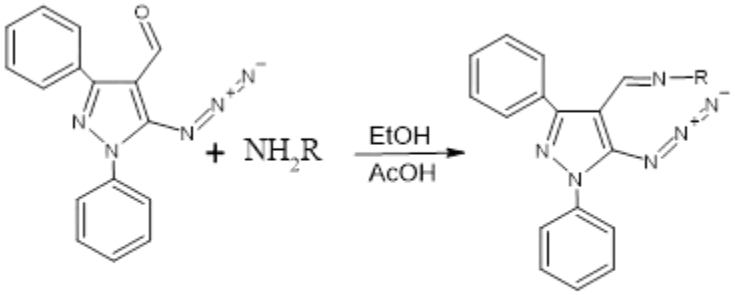
reaction until the 3-heteroarylchromones were completely consumed. The combination was then put into 100 millilitres of ice water and treated with 10% HCl to bring the pH down to 6-7. Using column chromatography on silica gel (dichloromethane), the white precipitate was filtered and purified, yielding products 4 in 75%-94% yields and 5 in 91%-96% yields. The novel compounds were 4a–4g[15].



R_1=H,4-ome,4-i-opr,4-OH; R_2=H, me, R_3=H,4-ome,4-OH,4-F, CF_3 ;Y=O ,S, N-Me

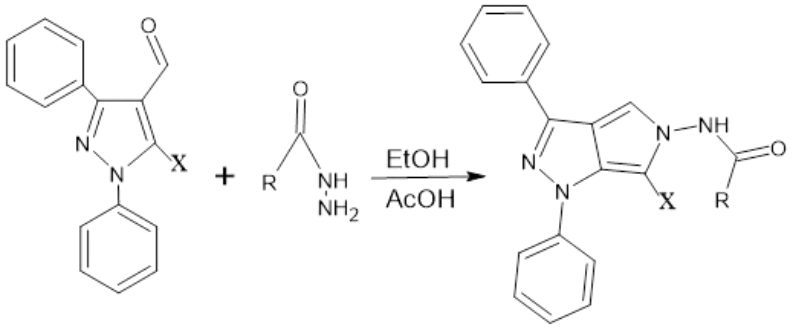
Scheme 1. General Synthetic Route for Compound 4and 5

2.2 Synthesis of N-[(5-Azido-1,3-diphenyl-1H-pyrazole-4-yl)- methylene]-N-arylamines (4a-c): Mahmoud F. Farhata et.al discussed of After dissolving 5-azido-1,3-di phenyl-1H-pyrazole-4-carbaldehyde (3) (0.5 g, 0.002 mol) in 25 ml of ethanol, 0.2 ml of glacial acetic acid and 0.002 mol of amine were added. Overnight, the reaction mixture was left to stand at room temperature. Filtration was used to separate the yellow crystalline precipitate (4a–c), which was then cleaned with cold ethanol[16]**.**



Scheme 2. Synthesis of 5-azidopyrazole-4-methylenearylamines (4a-c).

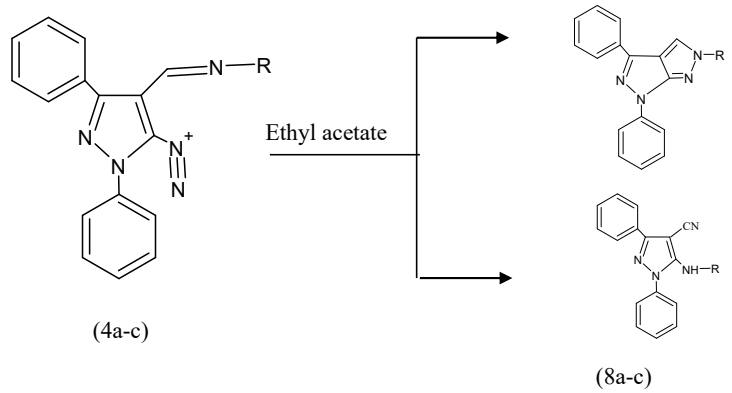
2.3 Synthesis of N-[(5-Substituted-1,3-diphenyl-1H-pyrazole-4 yl) methylene] hydrazides (5a-e): Five-azido-1,3-diphen-yl-1H-pyrazole-4-carbaldehyde (3) or five-chloro-1,3-diaryl 1H-pyrazole-4-carbaldehyde (2) (1.30 g, 0.005 mol) was dissolved in 15 ml of ethanol, followed by the addition of 0.2 ml of glacial acetic acid and 0.005 mol of acid hydrazide. The reaction mixture was then allowed to remain at room temperature for two hours. Filtration was used to separate the yellow crystalline precipitate (5a–e), which was then cleaned with ethanol. While the azido compounds (5d,e) were utilized without additional purification, the chloropyrrazole hydrazides (5a-c) were crystallized from ethanol.[16]



a: R = Ph, X = Cl; b: R = 4-Pyridyl, X = Cl c: R = CH_2CN, X = Cl; d: R = Ph, X = N_3 e: R = 4-Pyridyl, X = N_3

Scheme 3. Synthesis of *N*-[(5-substituted-1,3-diphenyl-1*H*-pyrazole-4-yl)- methylene] hydrazides (5a-e).

2.4 Synthesis of 5-Arylamino-1,3-diphenyl-1H-pyrazol-4 carbonitriles (8a-c): Five azido-1,3-diphenyl-1H-pyrazol-4-ylmethyl ene)-N-arylamine (4a-c) (0.0017 mol) was dissolved in fifteen milliliters of ethyl acetate and refluxed for four hours. After concentration, the solution was chilled. Filtration was used to collect the yellow solid, which was then allowed to dry in the air before crystallizing from pet-ether (bp. 60-80)/ethyl acetate 3:1.[16]

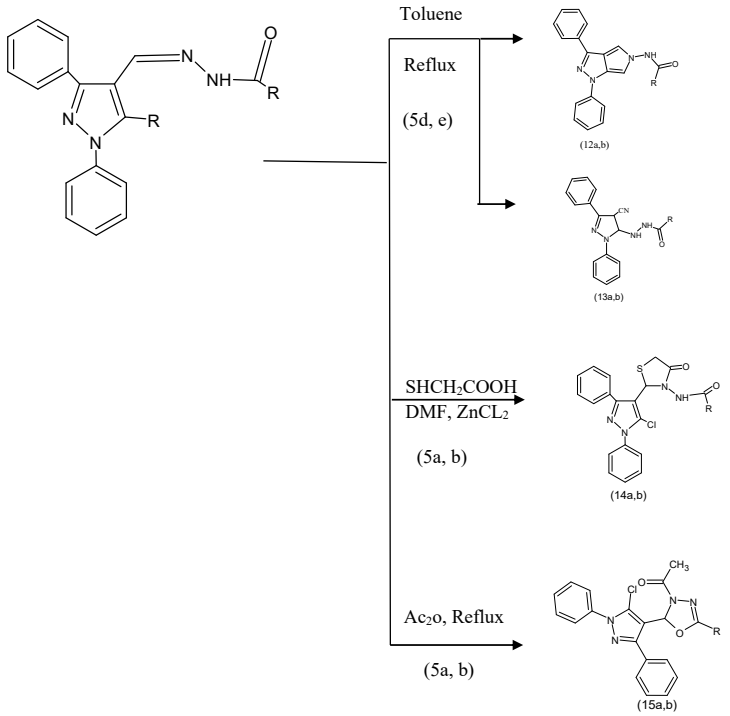


Scheme 4. Formation of 5-arylamino-1,3-diphenyl-1*H*-pyrazol-4-carbonitriles (8a-c)

2.5 Synthesis of N-(4-Cyano-1,3-diphenyl-1H-pyrazol-5-yl) hydrazide derivatives (13a,b): A solution of 5-azido 1,3-diphenyl-1H-pyrazol-4-yl)methylenehy drazides (5d,e) (0.0015 mol) in toluene (15 ml) was refluxed for 2h. The solution was concentrated and cooled and the yellow solid separated was collected by filtration, dried in air and crystallized from pet-ether (bp. 60-80)/ ethyl acetate 3:1.[16]

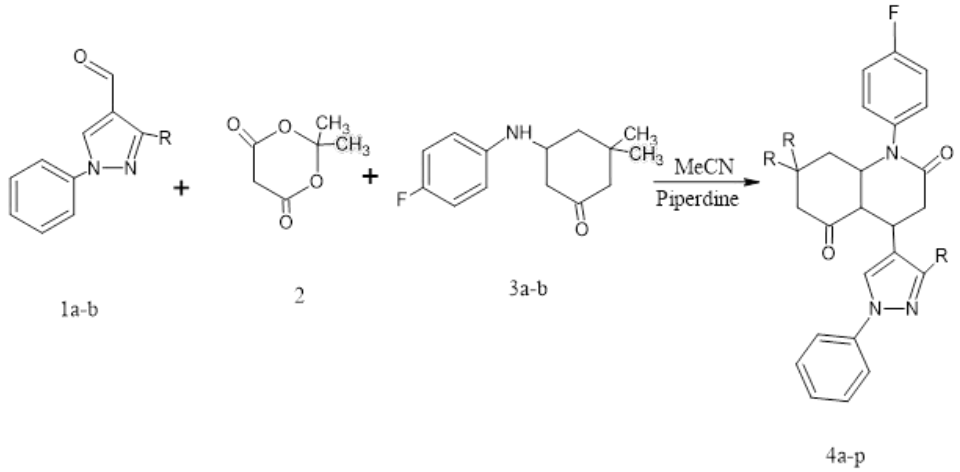
2.6 Synthesis of N-[2-(5-Chloro-1,3-diphenyl-1H-pyrazol-4 yl)-4-oxo-thiazolidin-3-yl]amides (14a,b): For six hours, N-[(5 chloro-1,3-diphenyl-1H-pyrazole-4-yl)methyl ene]hydrazide (5a,b) (0.015 mol) and thioglycolic acid (0.015 mol) were refluxed in 50 milliliters of N,N dimethylformamide (DMF) with a little amount of anhydrous ZnCl2. After cooling and pouring the reaction mixture over crushed ice, the resulting yellow solid was filtered out, cleaned with water, and crystallized from ethanol.[16]

2.7 Synthesis of 3-Acetyl-2-(5-chloro-1,3-diphenyl-1H-pyrazol 4-yl)-5-aryl-2,3-dihydro-1,3,4-oxadiazoles (15a, b): Excess acetic anhydride (10 ml) and N- [(5 chloro-1,3-diphenyl-1H-pyrazole-4-yl) methyl ene] hydrazide (5a, b) (0.00145 mol) was refluxed for two hours. After cooling, the reaction mixture was poured onto ice that had been crushed. After filtering, water washing, air drying, and crystallization from ethanol, the yellow precipitate was produced.[16]



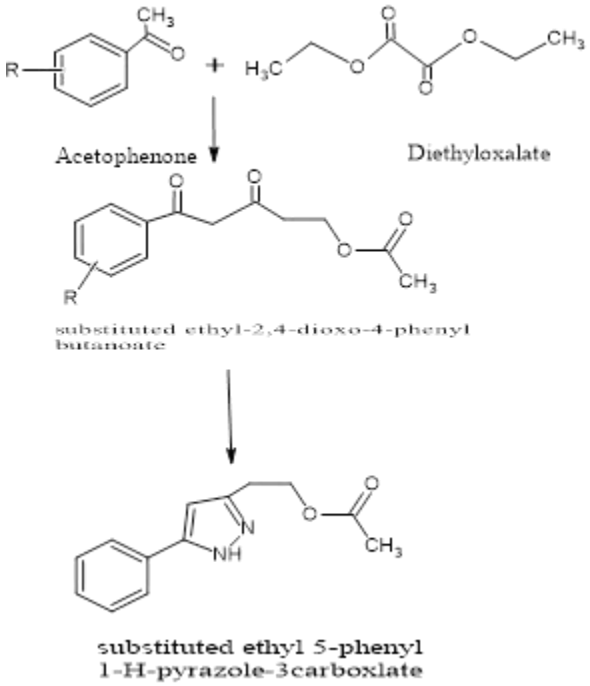
Scheme 7. Some reactions of (5-substituted-1,3-diphenyl-1H-pyrazol-yl) methylene hydrazides (5a, b,d, e).

2.8 Synthesis of 4-(3-(het)aryl-1-phenyl-1H pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-disubstituted 3,4,7,8-tetrahydroquinoline-2,5(1H,6H)-Dione: Nilesh J. Thumar • Manish P. Patel et.al synthesis In acetonitrile (20 ml) with three drops of piperidine, a combination of 1H-3-aryl-1-phenylpyrazole-4-carbaldehyde 1a–h (30 mmol), Meldrum's acid 2 (30 mmol), and suitable b-enaminone 3a–b (30 mmol) was gradually heated and refluxed for six hours while being stirred. Following the conclusion of the reaction, which was observed by TLC (ethyl acetate: toluene = 3:7), the reaction mixture was allowed to cool to room temperature. The separated solid was then filtered and cleaned using a 1:1 combination of methanol and chloroform to yield the pure compounds 4a–p. Below are the compounds 4a p's physical, analytical, and spectroscopic characterisation results.[17]



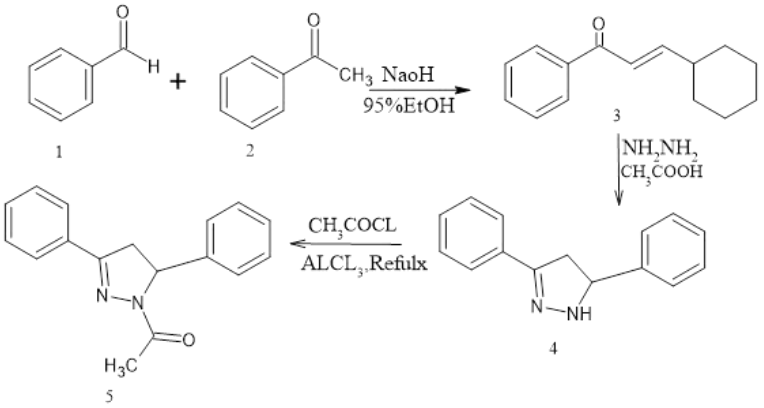
Scheme 8 Synthetic pathway for the synthesis of carbostyril derivatives of 1H-pyrazole 4a–p

2.9 Synthesis of substituted Ethyl 5-phenyl 1H-pyrazole-3-carboxylate: Gupta Sujeet Kumara et.al gives procedure A 15 mmol suspension of intermediate compound substituted ethyl 2,4-dioxo 4-phenyl-butanoates (1a-j) in glacial acetic acid (70 %, 10 ml) was mixed with a solution of hydrazine hydrate (99%, 15 mmol). The mixture was refluxed at 80–90°C for 6–8 hours. TLC kept track of the reaction's development. To get the appropriate pyrazole derivatives (2a-j), the product was filtered, cleaned with ethanol, dried, and recrystallized from ethyl acetate.[18]



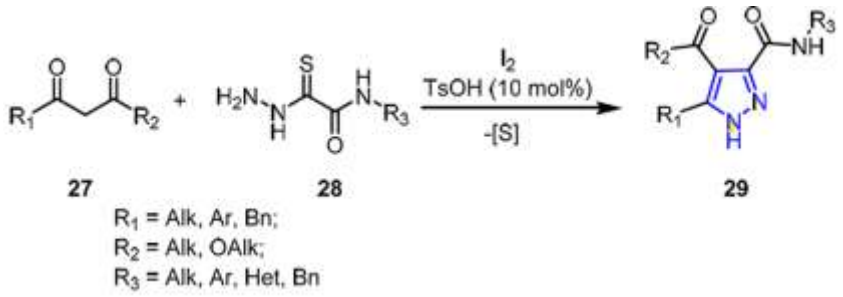
Scheme 9. Synthetic protocol of compounds (2a-j).

2.10 Synthesis of 1-acetyl-3,5-diphenyl-1H-pyrazole from Chalcone: Noor Hidayah Pungot1et.al synthesis After adding 3,5-Diphenyl 2-pyrazoline 4 to a flask containing 1.564 mmol of anhydrous AlCl3, 100 mL of acetyl chloride was added. For three hours, the reaction mixture was refluxed in a sealed tube at 65°C. Using the fractional crystallization technique, dichloromethane was used to purify the reaction after it had been agitated until all of the solids had dissolved. Then, under vacuum pressure, petroleum ether was added and filtered. After being oven-dried at 40°C, the crude product yielded a brownish solid in 0.4562 g (55%).[19]



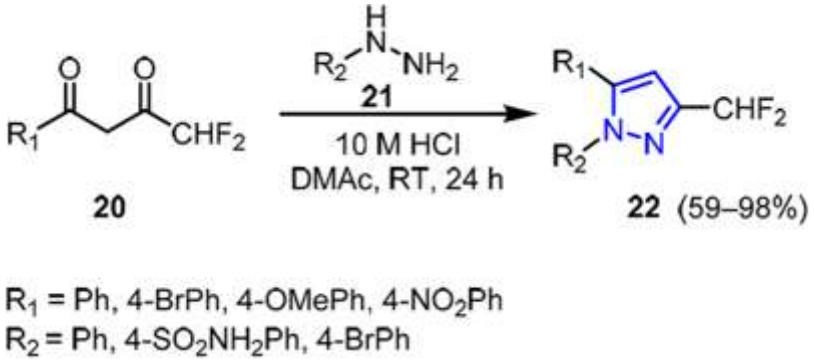
Scheme 10. Overall synthetic route to compound 5

2.11 Synthesis of 3,4-dicarbonyl-substituted pyrazoles: Komendantova and her team work devised an innovative method for the synthesis of 3,4-dicarbonyl-substituted pyrazoles. This approach involves the use of a broad array of 1,3-dicarbonyl compounds oxime acid Thio hydrazides in an iodine promoted cascade imination/halogenation/cyclization/ring. contraction reaction in the presence of catalytic amounts of TsOH, accompanied by sulphur elimination the result is a highly efficient and straightforward route to functionalized pyrazoles, utilizing readily available substrates and mild reaction conditions[23].



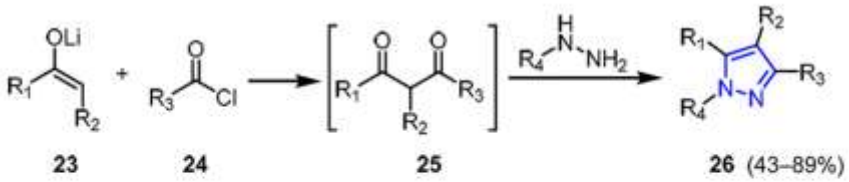
Scheme 11. Synthesis of substituted pyrazoles from 1,3–diketones and hydrazine derivative

2.12 Synthesis of 1-aryl-3,4,5-substituted pyrazoles: In their work, Gosselin et al. described a remarkably regioselective synthesis of 1–aryl–3,4,5–substituted pyrazoles, which involves the condensation of 1,3–diketones with arylhydrazines Notably, this reaction takes place efficiently at room temperature in N, N–dimethylacetamide, resulting in the formation of pyrazoles with high yields ranging from 59% to 98%. with arylhydrazines. [24].



Scheme 12. Synthesis of 3-trifluoromethyl-substituted pyrazoles.

2.13 Synthesis of 1,3 diketones from ketones and acid chlorides: In their study, Heller and Natarajan introduced a highly innovative approach to the synthesis of pyrazoles in situ. The process involved the direct synthesis of 1,3 diketones from ketones and acid chlorides, which were subsequently transformed into pyrazoles by the addition of hydrazine in good to excellent yields. This approach exhibits exceptional speed, generality, and chemo selectivity, enabling the synthesis of pyrazoles that were previously inaccessible, along with challenging pyrazole containing fused rings. The fusion of rapidity, generality, and chemo selectivity in this approach makes it a valuable asset in the arsenal of synthetic chemists, opening new avenues for the creation of diverse pyrazole-based compounds with enhanced complexity and utility[25].



R1 = Ph, 4-OMePh, 4-BrPh, Penthyl, 2,6-diOMePh, $N(Me)_2$Ph, 4-CNPh, 4-ClPh, 4-NO_2, 4-CO_2Et, Pyridinyl, Thiophenyl
R_2 = H, Ph, Propyl
R_3 = 4-BrPh, 4-OMePh, Penthyl, 6-ClPenthyl, 4-CNPh, 2-MePh, 4-MePh
R_4 = H, Me, Ph

Scheme 13. Synthesis of substituted pyrazoles from 1,3–diketones and hydrazine derivative

CONCLUSION:

In summary, various pyrazole have been synthesized in this review. The substituted pyrazoles are used in different sector. As result the techniques created for this chemical production are becoming increasingly significant. Lastly, several instances of pyrazole synthesis were given. The majority of research projects follow this set of guidelines. summary, while significant progress has been made in improving both the yield and efficacy of pyrazole products, ongoing research into more efficient, selective, and sustainable synthetic methods will be key to unlocking the full potential of pyrazoles in diverse applications.

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