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Review

Recent Advances in the Synthesis of Pyrazole Derivatives: A Review

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Abstract: Pyrazole, characterized by a five-membered heterocyclic structure featuring two neighboring nitrogen atoms, serves as a core element. Pyrazoles hold a privileged status as versatile frameworks in various sectors of the chemical industry, including medicine and agriculture. Previous reviews have extensively highlighted the significance of pyrazoles and their diverse biological activities, encompassing roles such as antituberculosis, antimicrobial, antifungal, anti-inflammatory, anticancer, and antidiabetic agents. Consequently, they have garnered substantial interest from researchers. 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. These methods span from utilizing transition-metal catalysts and photoredox reactions to employing one-pot multicomponent processes, novel reactants, and innovative reaction types. It encompasses studies conducted by numerous scientists worldwide, showcasing collective efforts in advancing the methodologies and applications of pyrazole derivatives.

Keywords: pyrazole derivatives; synthesis; reactions; heterocyclic; recent advances

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1. Introduction

Over the past decade, there has been a significant increase in interest in pyrazole chemistry, primarily driven by the discovery of fascinating properties demonstrated by numerous pyrazole derivatives. The term "pyrazole" was initially discovered by Ludwig Knorr in 1883 [1], while Edward Buchner is recognized as the first to synthesize it in 1889 [2]. Pyrazoles, as five-membered heterocycles, belong to a class of compounds highly valued in organic synthesis. Within the azole family, they are among the most extensively studied groups of compounds. Over the years, a vast array of synthesis methods and synthetic analogues have been documented, highlighting their significant importance in research and applications [3]. Furthermore, the pyrazole fragment plays a crucial role in numerous organic ligands and serves as an essential coordinator. Recent research has uncovered intriguing applications of the pyrazole structure in organic synthesis, where it acts as both a directing and transforming group [4,5]. Pyrazole serves as a fundamental element present in various small molecules, exhibiting a diverse array of agricultural and pharmaceutical activities [3]. Specifically, they are classified as inhibitors of protein glycation, exhibiting properties such as anti-inflammatory, antibacterial, antifungal, anticancer, antidiabetic, antioxidant, antidepressant, anti-tuberculosis, and antiviral activities [3,6–8]. Additionally, certain pyrazoles find applications in supramolecular and polymer chemistry, in the food industry, and are utilized as cosmetic colorings [8]. In recent years, a number of FDA-approved and commercially available drugs, both patented and non-patented, have been formulated using pyrazole derivatives [9] (Figure 1). This trend highlights the extensive

utilization of these groups in the creation of novel bioactive compounds. This review provides a succinct overview of pyrazole pharmacophore synthesis, making it a valuable reference guide for researchers exploring this field. The review is loosely organized into chemical synthesis categories.

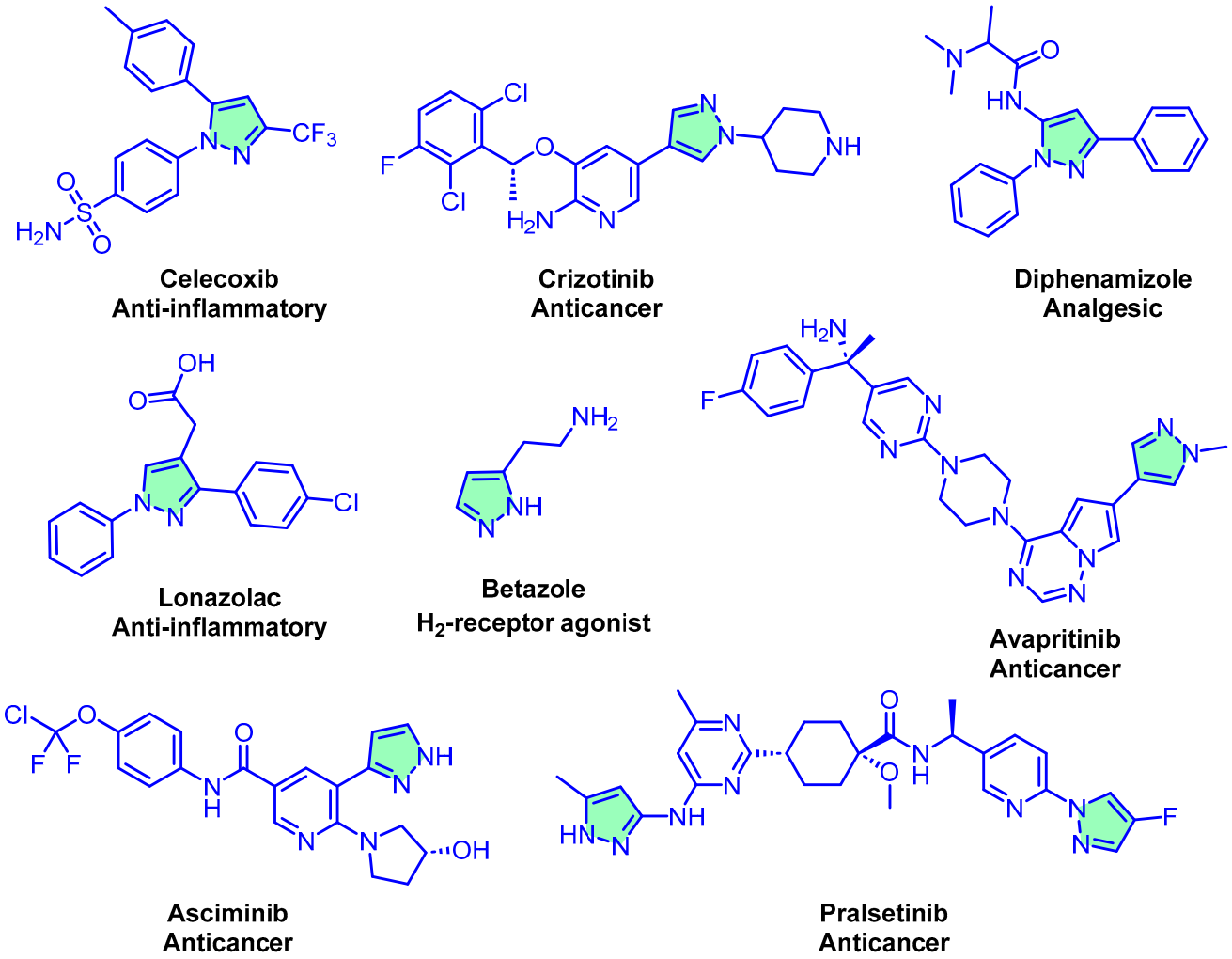


Figure 1. Pharmaceutical drugs containing pyrazole moiety.

2. The Primary Approaches for Obtaining the Pyrazole Nucleus

Pyrazole, as an aromatic heterocycle with π-electron excess, displays distinct reactivity patterns in organic chemistry. Nucleophilic attacks are favored at positions 3 and 5, while electrophilic substitution reactions preferentially take place at position 4 [10] (Figure 2).

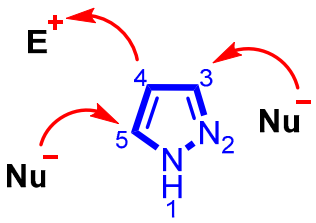


Figure 2. The pyrazole structure.

Unsubstituted pyrazole can be represented in three distinct tautomeric forms, as illustrated in Figure 3. This propriety adds to the versatility and complexity of pyrazole's chemical behavior and has significant implications in various chemical reactions and processes.

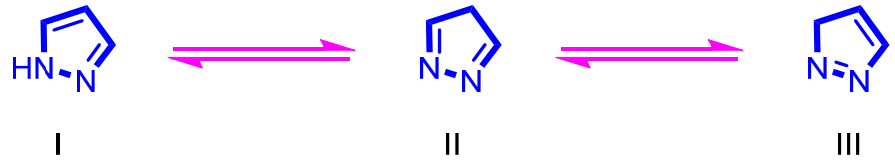


Figure 3. Tautomeric forms of unsubstituted pyrazole.

In the realm of organic chemistry, pyrazoles bearing diverse substitutions with aromatic and heteroaromatic groups exhibit a plethora of biological activities, making them exceptionally captivating. Since the first syntheses described by Knorr [1], the various approaches to accessing the pyrazole nucleus have undergone numerous modifications, advancing their synthetic versatility and potential applications in various fields. In this review, we will delve into this evolutionary process and explore the commonly employed methods to obtain substituted pyrazoles, namely:

- Cyclocondensation of hydrazine's and similar nuclei with carbonyl systems;
- Multicomponent reactions;
- Dipolar cycloadditions.

2.1. Cyclocondensation of Hydrazine and Its Derivatives on 1,3-Difunctional Systems

The primary approach utilized to obtain substituted pyrazoles involves a cyclocondensation reaction between a suitable hydrazine, acting as a bidentate nucleophile, and a carbon unit including, 1,3-dicarbonyl (**I**), α,β-unsaturated carbonyl compounds (**II**, **III**), and β-enaminones or related compounds (**IV**) (Figure 4).

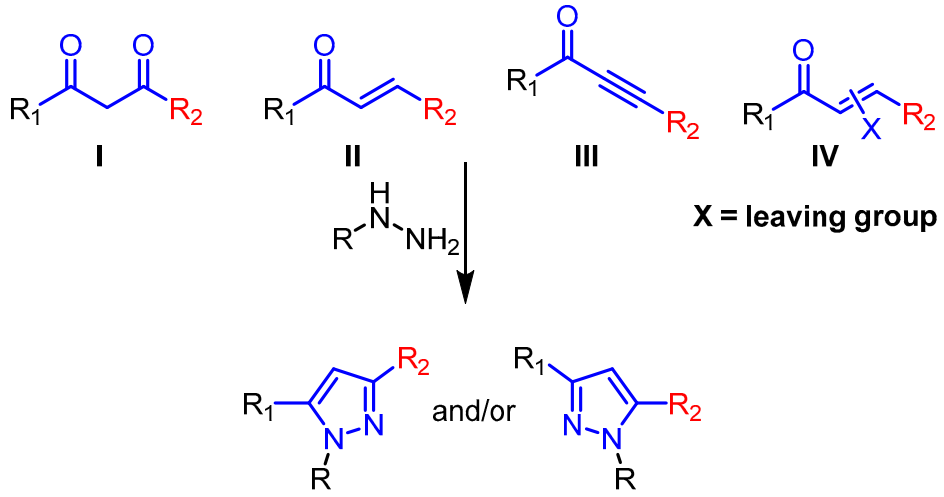


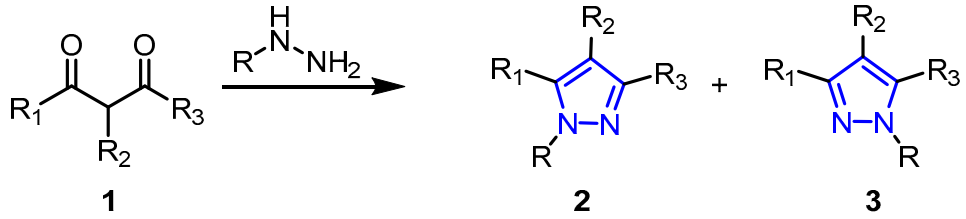
Figure 4. Examples of α,β-unsaturated carbonyl compounds.

2.1.1. Pyrazoles from 1,3-Diketones

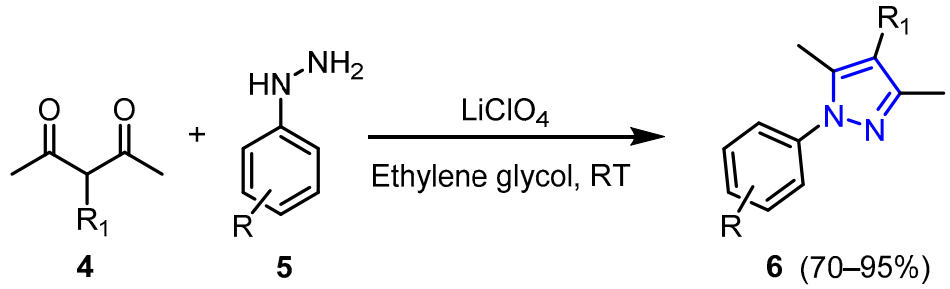
Cyclocondensation of hydrazine derivatives with 1,3-dicarbonyl compounds presents a straightforward and rapid method for obtaining polysubstituted pyrazoles. Knorr and his collaborators [1] accomplished the initial synthesis of substituted pyrazoles in 1883. They reacted hydrazine derivatives with β-diketones **1**, providing the formation of a mixture of two regioisomers **2** and **3**, where the substituted heteroatom is either next to the R_1 or the R_3 substituents (Scheme 1).

Konwar et al. [11] established an eco-friendly procedure for synthesizing pyrazole derivatives, employing lithium perchlorate as a Lewis acid catalyst. Initially, they react with acetylacetone and 2,4-dinitriphenylhydrazine as a model to determine the optimized reaction conditions. At first, they attempted the reaction solely with solvents, without adding any catalyst, but it did not proceed at all, highlighting the need for a catalyst. The synthetic pathway consisted of the reaction of hydrazines **5** with 1,3-diketones **4** in the

presence of ethylene glycol. Pyrazoles **6** were afforded in good to excellent yields (70–95%) at room temperature (Scheme 2, Table 1).



Scheme 1. The synthesis of polysubstituted pyrazoles using hydrazine derivatives and 1,3-dicarbonyl compounds.

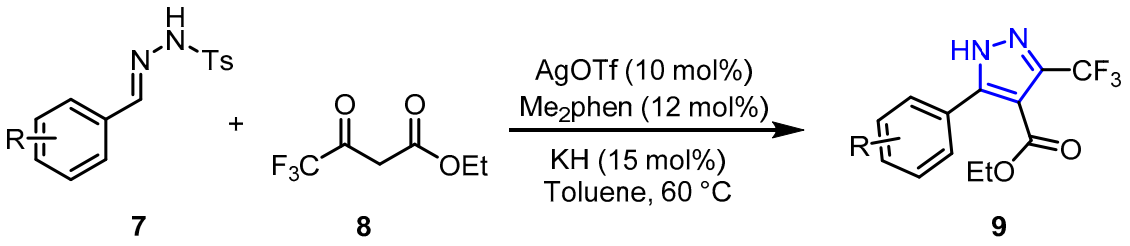


Scheme 2. Synthesis of 1,3,5-substituted pyrazoles from substituted acetylacetone.

Table 1. Effect of substituents on pyrazole synthesis.

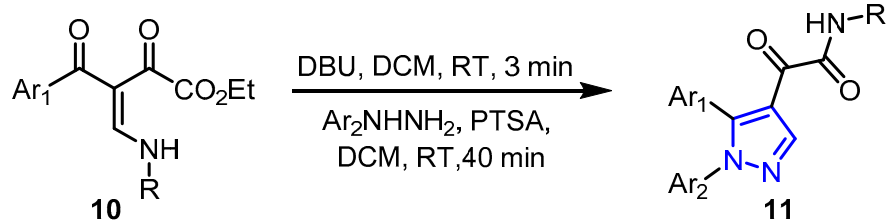
R	R_1	Yield	R	R_1	Yield (%)
2,4-diNO_2	H	92	4-CN	H	95
H	H	80	H	Me	90
4-Br	H	90	4-Me	Me	95
H	Cl	90	4-CN	Et	85
4-Me	Cl	95	4-NO_2	Me	87
4-Br	Cl	90	H	Et	92
4-NO_2	Cl	90	4-Me	Et	95
4-CF_3	Cl	80	4-Br	Et	80
4-CF_3	H	70	4-Cl	H	95
4-CN	Cl	90	4-Cl	Cl	90

Xu et al. [12] reported the synthesis of 5-aryl-3-trifluoromethyl pyrazoles, which involved a silver-catalyzed reaction using *N*′-benzylidene tolylsulfonohydrazides **7** and ethyl 4,4,4-trifluoro-3-oxobutanoate **8** as precursors. The process entailed sequential steps of nucleophilic addition, intramolecular cyclization, elimination, and ultimately, [1,5]-H shift, resulting in the formation of trifluoromethylated pyrazole derivatives **9** in yields ranging from moderate to excellent (Scheme 3). During the optimization process, the yield of the product improved when the reaction temperature was raised to 60 °C. However, increasing the temperature beyond 60 °C led to a decrease in the yield. The $Cu(OTf)_2$ transition catalyst resulted in a 60% yield, whereas $Fe(OTf)_3$ showed no productive outcome. In comparison to toluene, THF or dioxane provided a lower yield of the product. Additionally, K_2CO_3 exhibited higher effectiveness compared to NaH, *t*-BuOK, and *t*-BuONa. Furthermore, incorporating neocuproine as a ligand resulted in the most favorable performance with a yield exceeding 99%. In contrast, employing 2,2′-bipyridine or 1,10-phenanthroline as ligands led to lower yields of 57% and 92%, respectively.



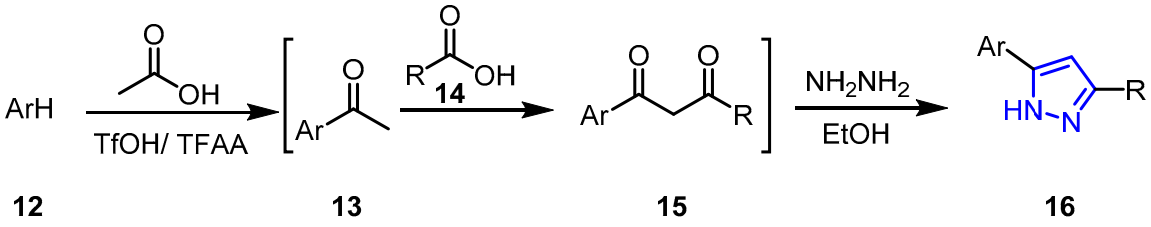
Scheme 3. Synthesis of 5-aryl-3-trifluoromethyl pyrazoles in the presence of a silver catalyst.

Poletto and collaborators described a one-pot synthetic strategy to produce highly regioselective α-ketoamide *N*-arylpyrazoles **11**, utilizing secondary β-enamine diketone **10** and arylhydrazines as precursors [13]. Significantly, the in situ-produced intermediate 4-acyl 3,5-dihydroxypyrrolone underwent nucleophilic substitution at C-5 by arylhydrazine. Subsequently, heterocyclization took place at the carbonyl carbon of the acyl group (refer to Scheme 4).



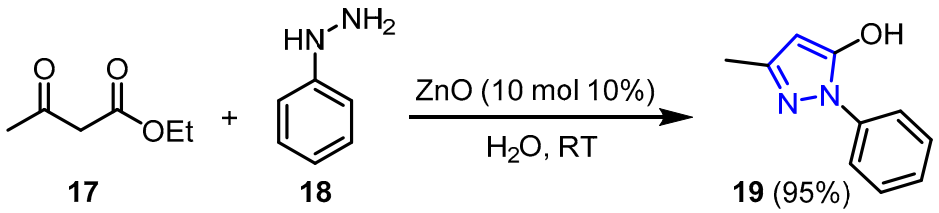
Scheme 4. The synthetic route of arylpyrazoles using secondary β-enamino diketone and arylhydrazine.

In their research, Kim et al. [14] devised a swift and effective "one-pot" method for synthesizing pyrazoles from (hetero)arenes and carboxylic acids. The procedure involves the sequential formation of ketones, β-diketones, and subsequent heterocyclization with hydrazine. Our initial assumption was that three straightforward steps could lead us to 3,5-disubstituted pyrazoles **16**. First, the TfOH/TFAA-mediated "one-pot" synthesis of 1,3-diketones **15** from methylarylketones **13**, utilizing arenes **12** and carboxylic acids **14**. Then, the conversion of dicarbonyl compounds **15** to 3,5-disubstituted pyrazoles **16** was carried out under Knorr reaction conditions (see Scheme 5).



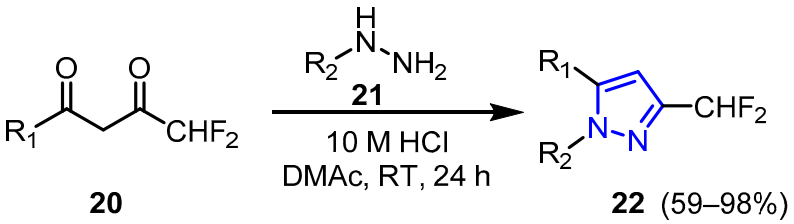
Scheme 5. The synthetic route of pyrazoles from arenes and carboxylic acids via 'one-pot' synthesis.

Girish et al. [15] conducted a remarkable study where they introduced a highly efficient and environmentally friendly approach using nano-ZnO catalyst for synthesizing 1,3,5-substituted pyrazole derivatives **19**. The process involved the condensation of phenylhydrazine **18** with ethyl acetoacetate **17** under controlled conditions (see Scheme 6). The key advantages of this method include its exceptional yield, reaching an impressive 95%, short reaction time, and straightforward work-up procedure. The combination of excellent yield, short reaction time, and ease of handling makes this method a promising and valuable addition to the field of pyrazole derivative synthesis.



Scheme 6. Synthesis of 3-methyl-1-phenyl-*1H*-pyrazol-5-ol using Nano-ZnO as catalyst.

In their work, Gosselin et al. [16] described a remarkably regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles **22**, which involves the condensation of 1,3-diketones **20** with arylhydrazines **21** (see Scheme 7). 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%.

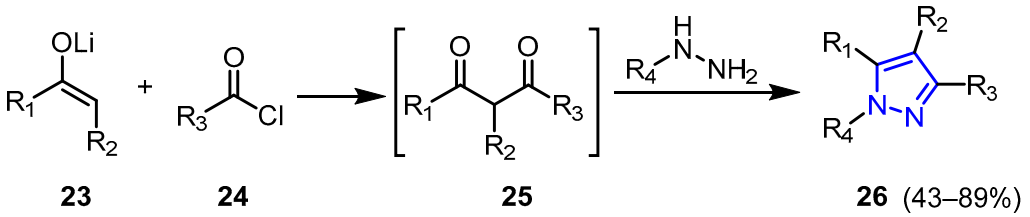


R_1 = Ph, 4-BrPh, 4-OMePh, 4-NO_2Ph
R_2 = Ph, 4-SO_2NH_2Ph, 4-BrPh

Scheme 7. Synthesis of 3-trifluoromethyl-substituted pyrazoles.

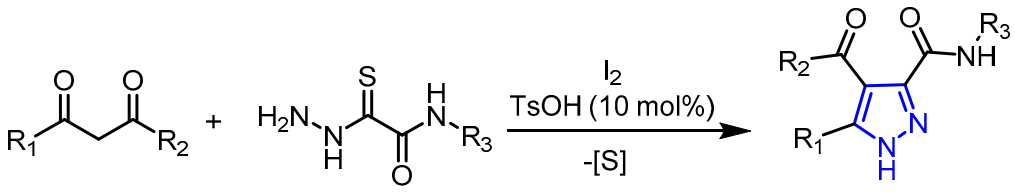
In their study, Heller and Natarajan [17] introduced a highly innovative approach to the synthesis of pyrazoles in situ. The process involved the direct synthesis of 1,3-diketones **25** from ketones **23** and acid chlorides **24**, which were subsequently transformed into pyrazoles **26** by the addition of hydrazine in good to excellent yields (see Scheme 8). This approach exhibits exceptional speed, generality, and chemoselectivity, enabling the synthesis of pyrazoles that were previously inaccessible, along with challenging pyrazole-containing fused rings. The fusion of rapidity, generality, and chemoselectivity 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.

Komendantova and her team work devised an innovative method for the synthesis of 3,4-dicarbonyl-substituted pyrazoles **29** [18]. This approach involves the use of a broad array of 1,3-dicarbonyl compounds **27** and oxamic acid thiohydrazides **28** in an iodine-promoted cascade imination/halogenation/cyclization/ring contraction reaction in the presence of catalytic amounts of TsOH, accompanied by sulfur elimination (see Scheme 9). The result is a highly efficient and straightforward route to functionalized pyrazoles, utilizing readily available substrates and mild reaction conditions.



R1 = Ph, 4-OMePh, 4-BrPh, Penthyl, 2,6-diOMePh, $N(Me)_2Ph$, 4-CNPh, 4-ClPh, $4\text{-}NO_2$, $4\text{-}CO_2Et$, 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

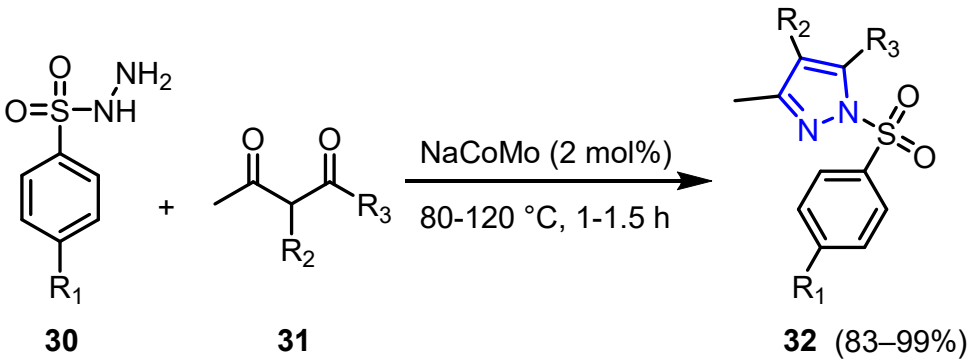
Scheme 8. Synthesis of substituted pyrazoles from 1,3-diketones and hydrazine derivatives.



R_1 = Alk, Ar, Bn;
R_2 = Alk, OAlk;
R_3 = Alk, Ar, Het, Bn

Scheme 9. Synthesis of substituted pyrazoles from 1,3-diketones and hydrazine derivatives.

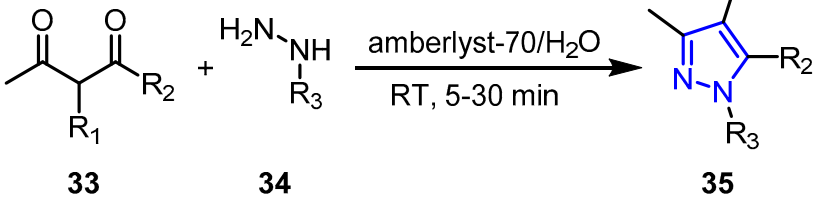
Yan et al. [19] made a remarkable discovery by uncovering a new metal-oxo-clusters-based inorganic framework called "3D platelike ternary-oxo-cluster" (NaCoMo), which serves as an efficient catalyst for generating novel pyrazole derivatives. Moreover, this catalyst exhibits exceptional catalytic activity in the condensation and cyclization reaction of sulfonyl hydrazides **30** and 1,3-diketones **31** to synthesize the pyrazoles **32**, leading to an impressive yield of up to 99% for the desired product (see Scheme 10). The successful synthesis of NaCoMo signifies the introduction of a new type of non-classical polyoxometalates.



R_1 = H, Me, OMe, Cl, Br, NO_2
R_2 = H, Cl, Me
R_3 = Me, Cyclopropyl

Scheme 10. Synthesis of substituted pyrazoles using NaCoMo as catalyst.

Chandak and his collaborators documented an environmentally friendly and efficient aqueous synthesis of pyrazoles **35** via the condensation of hydrazines or hydrazides **34** with 1,3-diketones **33** at room temperature, utilizing Amberlyst-70 as the catalyst (see Scheme 11) [20]. This innovative protocol benefits from the use of resinous, nontoxic, thermally stable, and cost-effective Amberlyst-70 as a heterogeneous catalyst, in addition to offering a simple reaction workup, thus presenting valuable eco-friendly attributes.

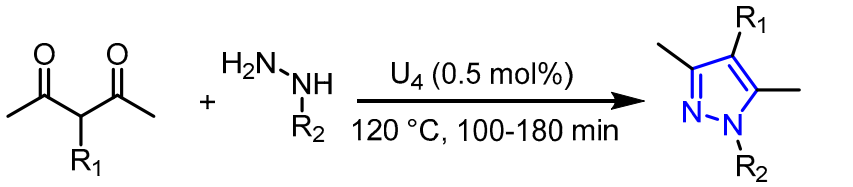


33 **34** **35**

R_1	R_2	R_3	Yield (%)
H	Me	Ph	94
Me	OEt	Ph	85
Cl	OEt	Ph	97
H	OEt	Ph	80

Scheme 11. Amberlyst-70 catalyzed the synthesis of pyrazole derivatives.

Liu et al. [21] made an exciting discovery of a novel Keggin-based U-POW (U(VI)-containing polytungstates) tetramer, referred to as U_4. This tetramer showcased remarkable bifunctional Lewis's acid-base catalytic properties and exhibited excellent performance in the synthesis of pyrazoles **38** via the condensation of diverse hydrazines **37** with 1,3-diketones **36** under mild reaction conditions (see Scheme 12). This groundbreaking work not only presents a rare case of tetrameric U-POWs but also highlights the application of U-POWs in catalytic synthesis chemistry, potentially advancing the fields of POM (actinide-containing polyoxometalates) chemistry, actinide chemistry, and catalytic chemistry.



36 **37** **38** (91–99%)

R_1 = H, Me, Cl
R_2 = Ph, Penthyl, PhCO, 4-MePhCO, 4-OMePhCO, 4-FPhCO, 4-ClPhCO, 4-BrPhCO

Scheme 12. Synthesis of pyrazole derivatives catalyzed by U_4.

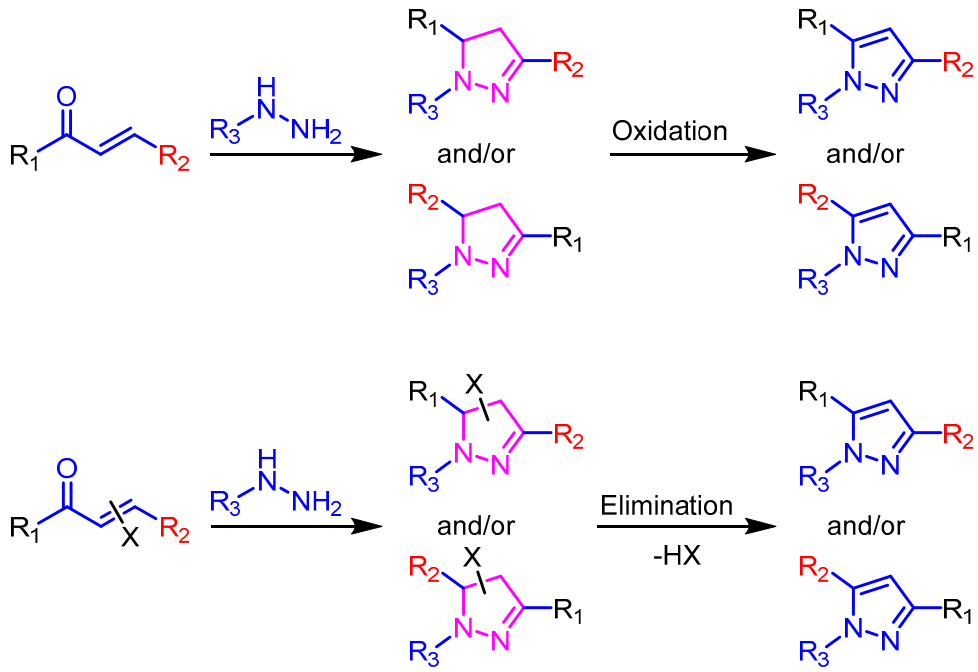
2.1.2. Pyrazoles from Vinyl Ketones and Vinyl Ketones Having a Leaving Group

As a general trend, the condensation of hydrazines with R-enones predominantly yields pyrazolines in a regioselective manner. Subsequently, to acquire the corresponding pyrazoles, these pyrazolines must undergo oxidation (see Scheme 13).

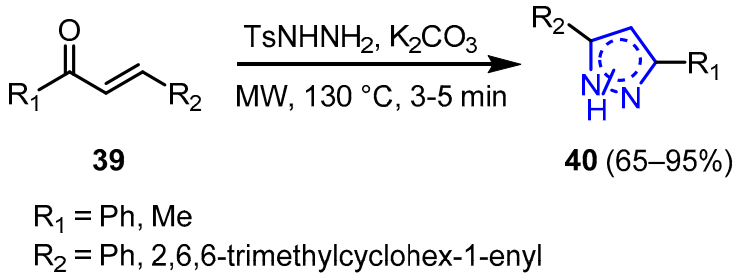
The α,β-Vinyl ketones that possess a leaving group can undergo a reaction with hydrazine derivatives, leading to the formation of pyrazolines. Subsequently, by eliminating the leaving group, the desired pyrazoles are generated (see Scheme 13).

The Corradi group conducted a study under microwave irradiation and solvent-free reaction conditions, wherein they successfully synthesized novel 3,5-disubstituted-*1H*-pyrazoles **40** [22] (see Scheme 14). This was achieved via the cycloaddition of tosylhydrazones and α,β-unsaturated carbonyl compounds containing a β-hydrogen **39**. The cycloaddition reaction was investigated using three different ketones: trans-4-phenyl-3-buten-2-one, β-ionone, and trans-chalcone. Notably, the corresponding 3,5-disubstituted-*1H*-pyrazoles **40** were obtained in high yields and with short reaction times. To assess the environmental impact, the proposed synthetic route was compared to the classical

synthetic route, aiming to provide a reliable methodology and tool for measuring their ecological implications.

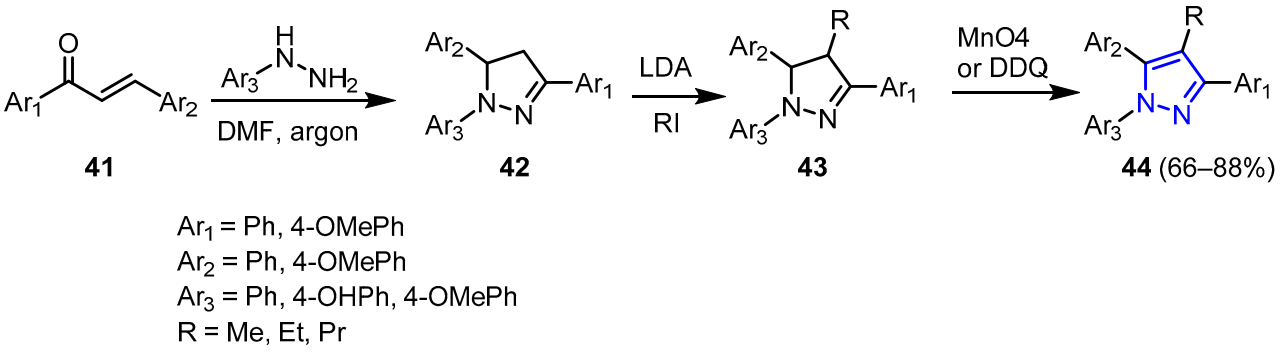


Scheme 13. The synthetic pathway to pyrazole derivatives via cyclocondensation reaction of α,β-ethylenic ketone, α,β-ethylenic ketone with a leaving group.



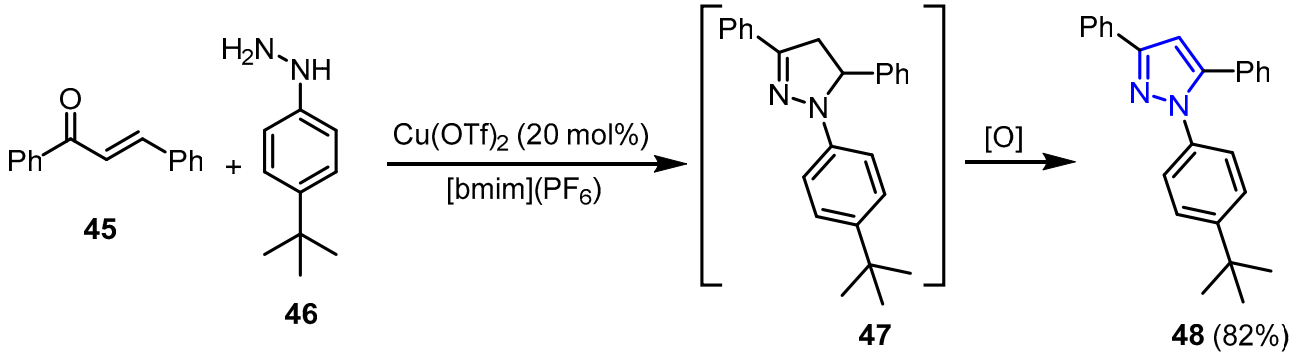
Scheme 14. Microwave-assisted one-pot synthesis of pyrazole derivatives.

Huang and Katzenellenbogen [23] successfully obtained a series of 4-alkyl-1,3,5-triarylpyrazoles **44** in a regioselective manner via the oxidation of pyrazolines **43**. These pyrazolines were initially prepared via a cyclocondensation reaction between phenyl and 4-methoxyphenylhydrazine and chalcones **41**, followed by alkylation at the C-4 position of the pyrazoline ring in **42** (see Scheme 15).



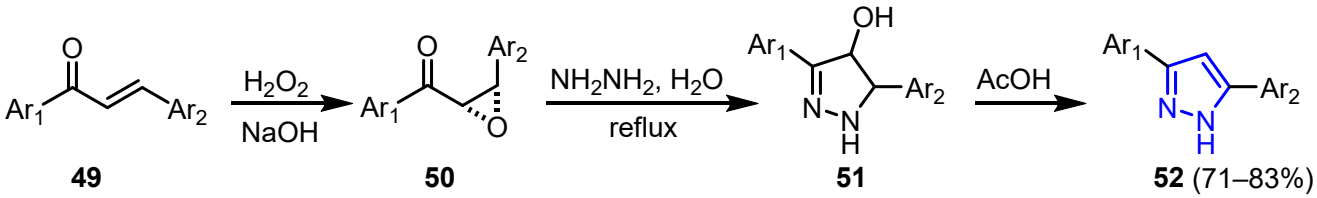
Scheme 15. Regioselective synthesis of 4-alkyl-1,3,5-triarylpyrazoles **44**.

In their study, Rao and his collaborators demonstrated a condensation reaction of an α,β-ethylenic ketone **45** with p-(4-(tert-butyl)phenyl) hydrazine **46** using copper triflate and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] (PF_6) as catalysts, leading to the formation of pyrazoline **47**. Subsequent in situ oxidation of this pyrazoline yielded the corresponding 1,3,5-trisubstituted pyrazole **48** [24] (see Scheme 16). The reaction protocol facilitated the production of 1,3,5-triarylpyrazoles with good yields (approximately 82%) via a one-pot addition-cyclocondensation between chalcones and arylhydrazines, followed by oxidative aromatization without the need for an additional oxidizing reagent. Notably, the catalyst displayed remarkable recyclability, retaining its catalytic activity for more than four cycles without significant loss.



Scheme 16. Synthesis of the pyrazole **48** catalyzed by [bmim] (PF_6).

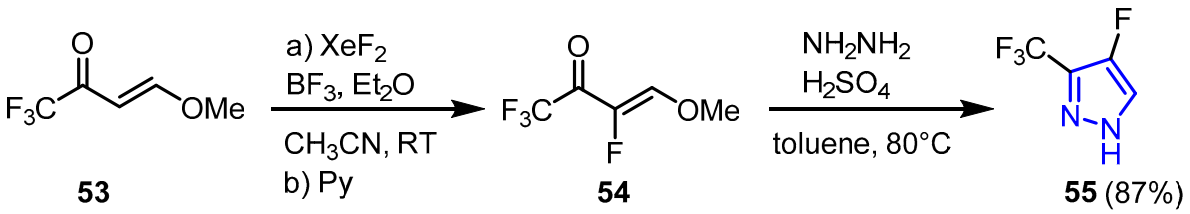
Another study described by Bhat and his team work consists of the synthesis of 3,5-diaryl-*1H*-pyrazoles starting with β-arylchalcones **49**. The process involved the reaction with hydrogen peroxide, leading to the formation of epoxides **50**. Following this, the addition of hydrazine monohydrate resulted in pyrazoline intermediates **51**, which upon dehydration yielded the desired 3,5-diaryl-*1H*-pyrazoles **52** [25] (see Scheme 17).



Ar_1 = Ph, 4-OMePh
Ar_2 = Ph, 4-OMePh, HCO, 3-OMePh, 4-FPh

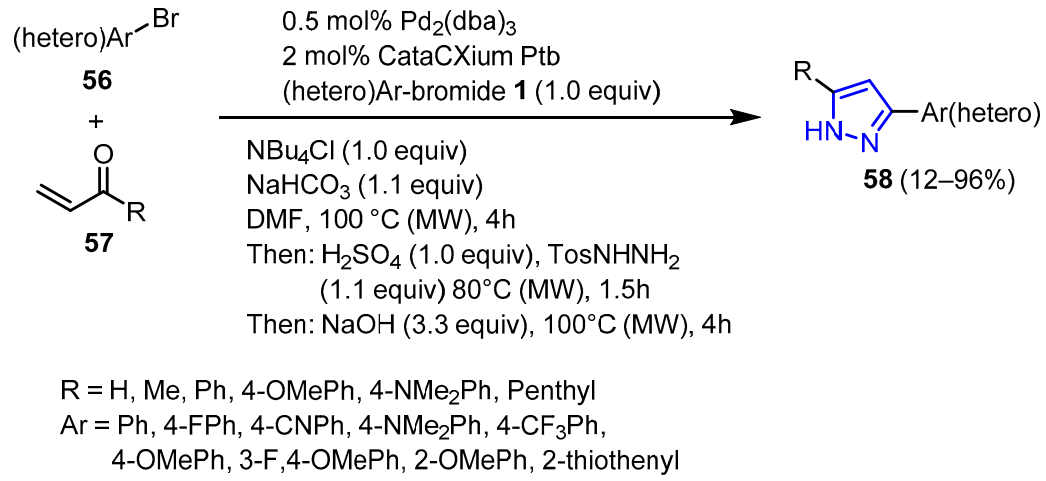
Scheme 17. The synthetic pathway to 3,5-diaryl-*1H*-pyrazoles **52**.

In 2020, Gerus et al. [26] conducted a study on the fluorination of enone **53** using XeF_2 in the presence of $BF_3{\cdot}Et_2O$. The addition of pyridine to the reaction mixture resulted in the formation of fluoroenone **54**, achieving a yield of 68%. Subsequently, the reaction of fluoroenone **54** with hydrazine sulfate yielded fluoropyrazole **55**, demonstrating an impressive yield of 87% (see Scheme 18).



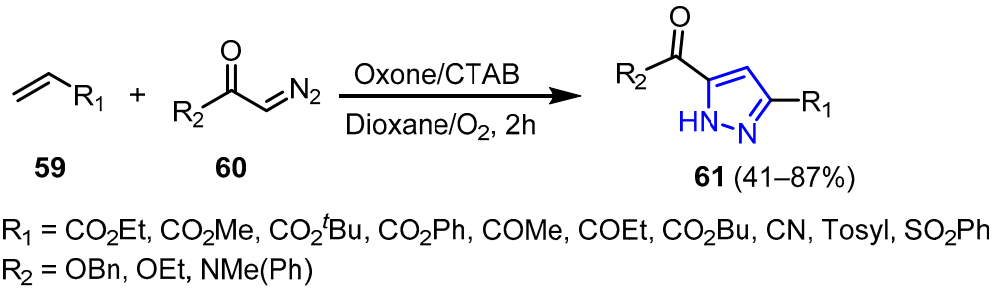
Scheme 18. The synthetic pathway to fluoropyrazole **55**.

Stephan and his co-workers made a groundbreaking discovery by unveiling a novel method for synthesizing pyrazole derivatives [27]. Initially, they efficiently synthesized 3-(hetero)aryl propenals and propenones using a Heck reaction involving (hetero)aryl bromides **56** and acrolein or vinyl ketones **57**. This reaction was carried out under a combination of Jeffery's and Fu's conditions, utilizing Beller's CataCXium Ptb ligand. The resulting 3-substituted α,β-unsaturated carbonyl derivatives served as valuable three-carbon building blocks. Using this straightforward approach, they successfully synthesized 3-(hetero)aryl and 3,5-diarylpyrazoles **58** with a broad range of substitution patterns via consecutive three- and pseudo-four-component syntheses, achieving modest to excellent yields (see Scheme 19). This concise and modular methodology proves to be highly suitable for preparing substance libraries of diversified pyrazoles.



Scheme 19. Synthesis of 3(5)-substituted pyrazoles **58**.

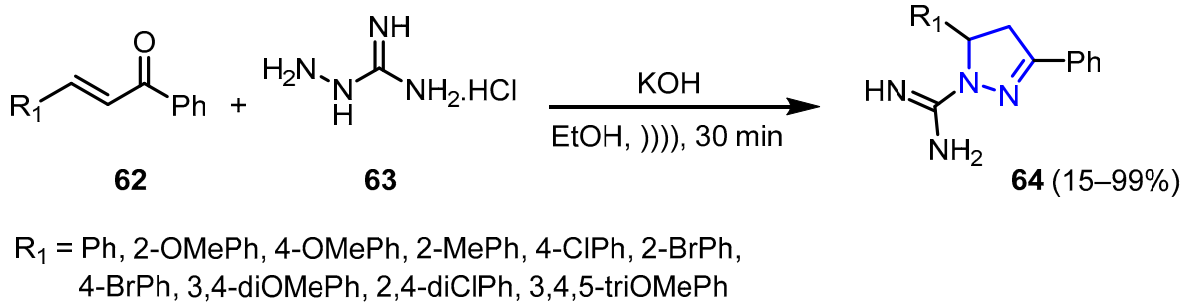
Paul Raj et al. [28] established a highly efficient protocol for synthesizing pyrazoles **61** via the oxidative [3 + 2] cycloaddition of electron-deficient terminal olefins **59** with α-diazoesters and amides **60**, using Oxone and cetyltrimethyl ammonium bromide (CTAB) as catalysts (see Scheme 20). Notably, this protocol offers several key advantages, including shorter reaction times, moderate to excellent yields, and good regioselectivity.



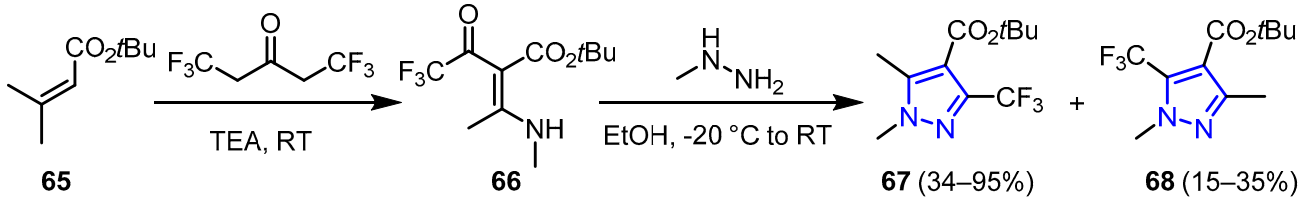
Scheme 20. Synthesis of 3,5-substituted pyrazoles using CTAB as catalyst.

Pizzuti and his research team synthesized a series of innovative 3,5-diaryl-4,5-dihydro-*1H*-pyrazole-1-carboximidamides **64** using a convenient and high-yielding method [29]. The process involved the utilization of chalcones **62** and aminoguanidine hydrochloride **63** under ultrasonic irradiation, as shown in Scheme 21.

Iminov and his colleagues devised a method to obtain the pyrazole moiety. It consists of the acylation of tert-butyl 3-(methylamino)but-2-enoate **65** using fluorinated acetic acid anhydrides at the enamine carbon atom [30]. Subsequently, the resulting product **66** was reacted with alkyl hydrazines, leading to mixtures of isomeric pyrazoles. These mixtures were separated via column chromatography to provide compounds **67** and **68**, yielding moderate to poor results in terms of yields (see Scheme 22).

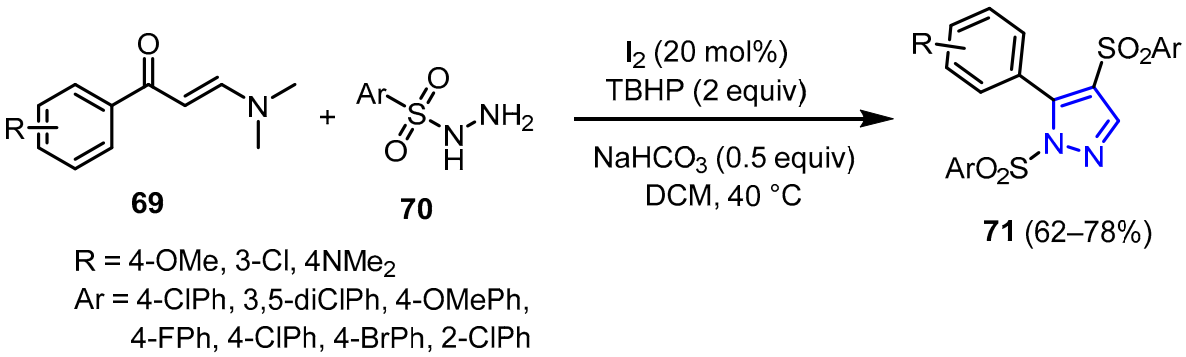


Scheme 21. Synthesis of 3,5-diaryl-4,5-dihydro-*1H*-pyrazole-1-carboximidamides **64** under ultrasonic irradiation.



Scheme 22. Synthetic routes for pyrazoles **67** and **68**.

Tian et al. [31] devised a practical protocol to synthesize 4-sulfonyl pyrazoles. They achieved this by reacting readily available *N*,*N*-dimethyl enaminones **69** with sulfonyl hydrazines **70** under the catalysis of molecular iodine in the presence of TBHP and $NaHCO_3$ at room temperature. The resulting pyrazole products **71** were formed via a tandem C(sp^2)-H sulfonylation and pyrazole annulation process, without requiring any transition metal catalyst or reagent (see Scheme 23). This innovative approach offers a convenient and efficient method for constructing novel pyrazoles containing a sulfonyl side chain in the heterocycle.

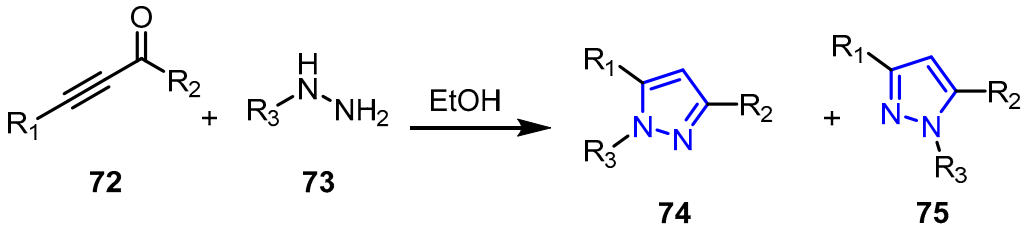


Scheme 23. Synthetic routes for pyrazoles **71** using I_2/TBHP, $NaHCO_3$ as catalyst.

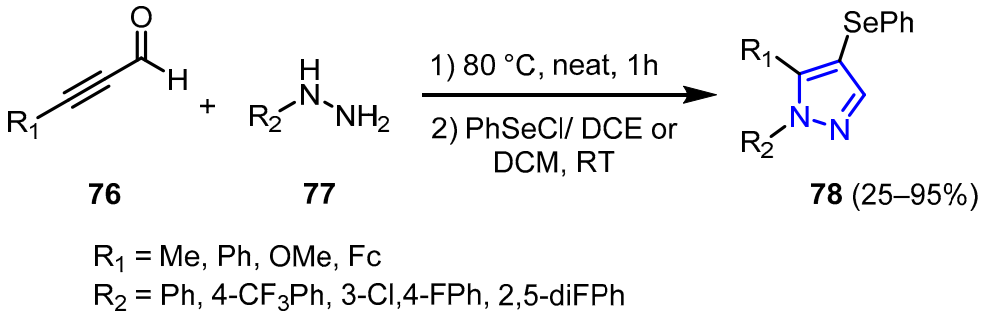
2.1.3. Pyrazoles from Acetylenic Ketones

The formation of pyrazoles via the cyclocondensation reaction of hydrazine derivatives **73** with acetylenic ketones **72** has been a well-known process for over a century [32]. However, despite its long-standing recognition, the reaction continues to yield a mixture of two regioisomers, namely **74** and **75** (as shown in Scheme 24).

Zora and his research group reported a comprehensive synthetic approach for the preparation of selenium-containing pyrazoles, specifically 4-(phenylselanyl)pyrazoles **78** [33]. The method involves reacting α,β-alkynic aldehydes **76** with hydrazines **77**, followed by the addition of phenylselenyl chloride. This one-pot reaction enables the in situ formation of α,β-alkynic hydrazones, which undergo cyclization upon direct treatment with phenylselenyl chloride, leading to the formation of 4-(phenylselenyl)pyrazoles **78** (see Scheme 25).

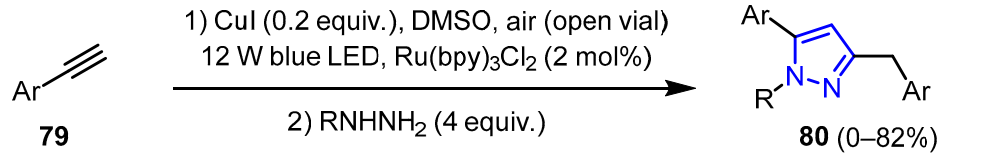


Scheme 24. Synthetic routes for the regioisomers **74** and **75** using cyclocondensation reaction of hydrazine derivatives **73** on the acetylenic ketones **72**.



Scheme 25. Synthetic routes for pyrazoles **78** via one-pot reaction.

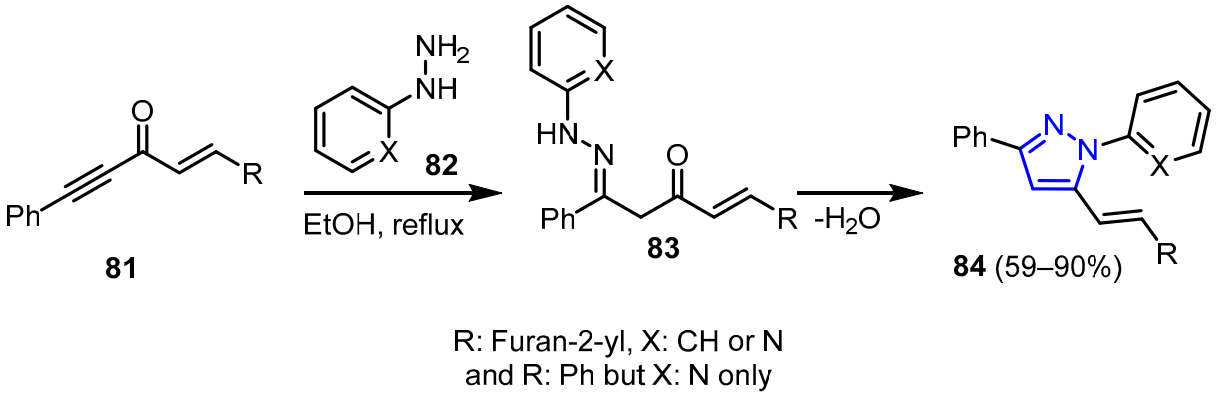
Meng et al. [5] introduced a novel visible-light-promoted cascade of Glaser coupling/annulation, enabling the one-pot synthesis of polysubstituted pyrazoles **80** from alkyne **79** and hydrazine derivatives (see Scheme 26). This method stands out due to its mild reaction conditions, utilization of readily available starting materials, and the eco-friendly oxidant, O_2. Notably, it exhibits excellent functional group tolerance and efficiency while accommodating a wide range of substituted phenyl acetylenes and hydrazines. The proposed mechanistic pathways involve photochemical irradiation, intramolecular hydrogen-atom-abstraction (HAT), and enamine-to-imine tautomerization to elucidate the underlying transformation steps.



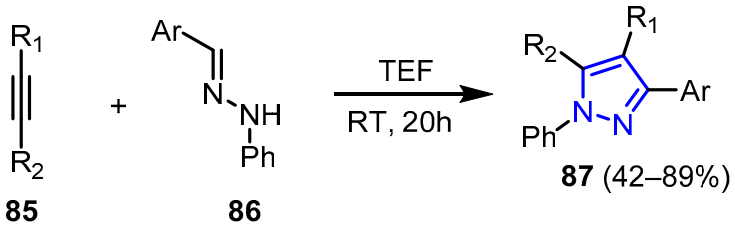
Scheme 26. Synthetic routes for pyrazoles **80** via one-pot reaction.

Golovanov and colleagues conducted a study focusing on the synthesis of substituted pyrazoles. They achieved this via the cyclocondensation of cross-conjugated enynones, dienynones, and trienynones **81** with arylhydrazines **82**, resulting in the regioselective synthesis of pyrazole derivatives **84**, including dihetaryl-substituted ethenes, buta-1,3-dienes, and hexa-1,3,5-trienes, or alternatively yielding 4,5-dihydro-1H-pyrazoles in good yield (Scheme 27).

Bhaskaran and his team devised a highly efficient, metal-free approach for synthesizing pyrazoles and chromenopyrazoles (**87**) using aldehyde hydrazones and acetylenic esters **86** [34]. This method allowed them to create a library of molecules with a wide range of functional groups, utilizing both symmetrical and unsymmetrical hydrazones and alkynes. The resulting derivatives were isolated in moderate to good yields (Scheme 28).



Scheme 27. The synthetic routes for pyrazoles **84**.

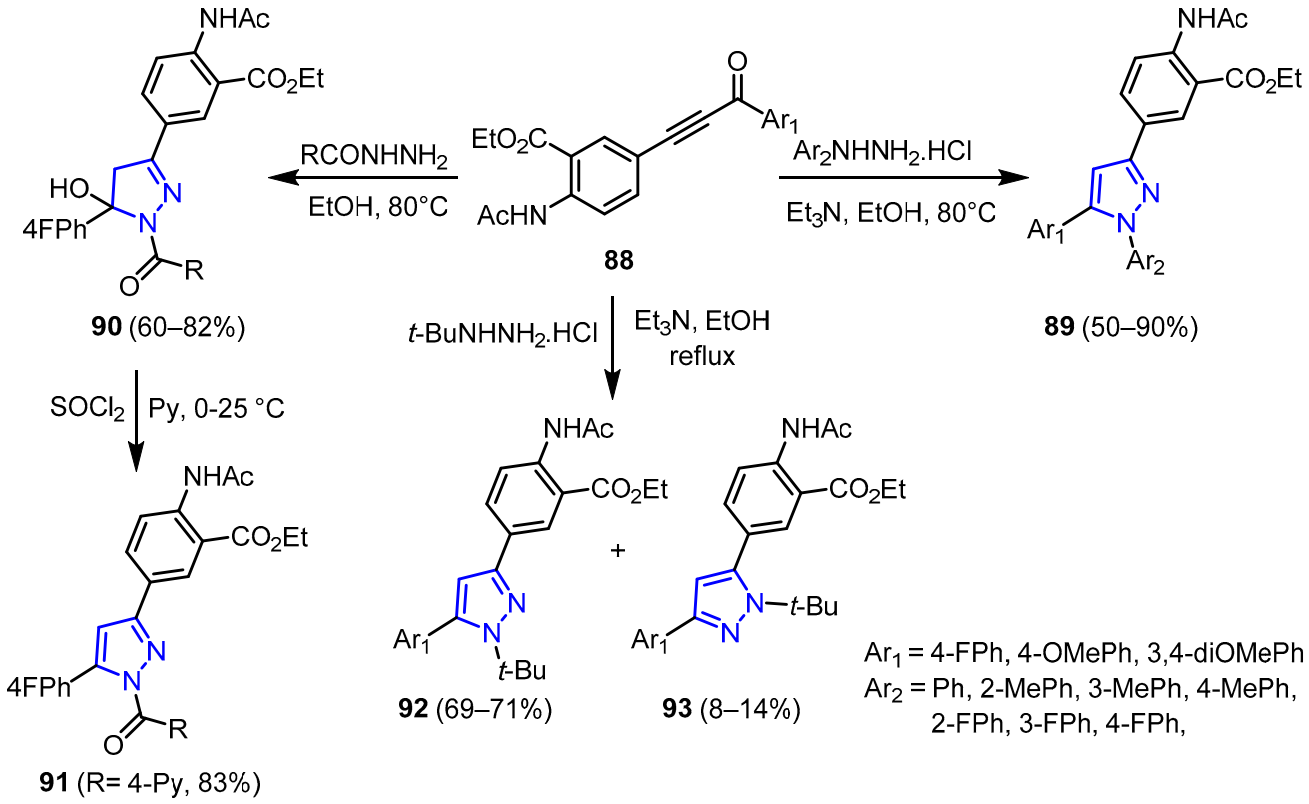


Scheme 28. The synthesis of pyrazole derivatives **87**.

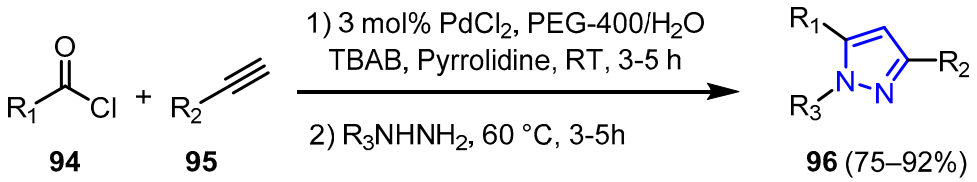
Savel'ev et al. [35] devised a highly effective method for synthesizing 1,3,5-trisubstituted pyrazoles using acetylenic ketones derived from ethyl 5-ethynylanthranilate in reactions with substituted hydrazines and hydrazides. During the study, they demonstrated that the cyclization of ethyl 5-(3-aryl-3-oxopropinyl)anthranilates **88** with arylhydrazines occurred with excellent regioselectivity, resulting in 1,3,5-trisubstituted pyrazoles **89** carrying an anthranilate moiety at position C-3. However, in the reactions of ethyl 5-(3-aryl-3-oxopropinyl)anthranilates with *N*-methyl- and *N*-tert-butylhydrazines, a significant deterioration of regioselectivity was observed **92** and **93**. In some cases, the initial products formed were 5-hydroxypyrazolines **90**. These 5-hydroxypyrazolines underwent dehydration in the presence of pyridine and thionyl chloride in benzene, eventually yielding the desired 1,3,5-trisubstituted pyrazoles **91**, as exemplified by the reactions of ethyl 5-[3-(4-fluorophenyl)-3-oxopropinyl]anthranilate with benzoyl and isonicotinoyl hydrazides (see Scheme 29).

Thirukovela and his team achieved a significant milestone in 2019 by developing an advanced one-pot regioselective synthesis of 3,5-disubstituted and 3,4,5-trisubstituted pyrazoles [36]. They employed a Cu-free protocol, utilizing in situ generated Pd-nanoparticles (PdNPs) as the catalyst in an environmentally friendly PEG-400/H_2O medium (see Scheme 30). This innovative approach represents a notable advancement in the field of pyrazole synthesis.

Topchiy et al. [37] demonstrated an efficient method for synthesizing 3-CF_3-pyrazoles **99** by employing a silver-catalyzed reaction between trifluoromethylated ynones **97** and aryl (alkyl) hydrazines **98**. The reaction exhibited remarkable speed, with rapid heterocyclization occurring within just 1 h at room temperature, utilizing AgOTf as the catalyst at a loading of 1 mol % (see Scheme 31). This process led to the highly regioselective formation of various 3-CF_3-pyrazoles, achieving exceptional yields of up to 99% for the isolated products. The researchers further investigated the reaction mechanism and discovered that it involves the formation of a hemiaminal as a crucial intermediate, shedding light on the underlying chemical pathways responsible for the synthesis of 3-CF_3-pyrazoles.

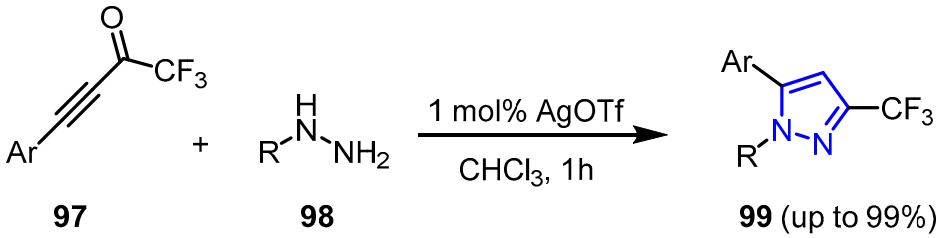


Scheme 29. The synthesis of pyrazole derivatives using ethyl 5-(3-aryl-3-oxopropinyl)anthranilates **88**.



R_1 = Ph, 4-MePh, 4-BrPh, 4-ClPh, 4NO_2Ph, 4-OMePh, Butyl
R_2 = Ph, 4-ClPh, 4-CNPh, 4-OMePh, 4-FPh, 4-ClPh, Furyl, Cyclohexyl
R_3 = H, Ph

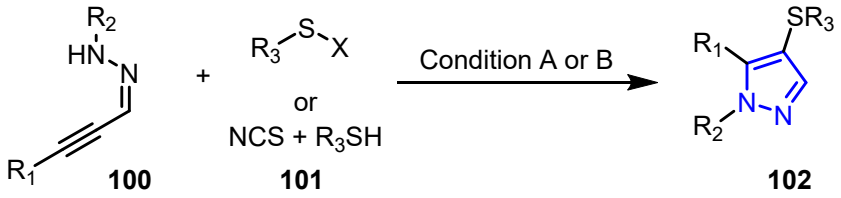
Scheme 30. One-pot regioselective synthesis of pyrazole derivatives **96**.



R = Ph, 4-MePh, 4-BrPh, C_6F_5, 4-HO_2CPh, 3-CF_3Ph, 2,6-diClPh,
4-CNPh, 4-OMePh, 4-NO_2Ph, Et, ^{t}Bu, 4-MePhSO_2, $CO_2{}^t$Bu
Ar = Ph, 4-MePh, 4-ClPh, 4-BrPh, 4-^{t}BuPh, 4-OMePh

Scheme 31. The synthesis of pyrazole derivatives **99** utilizing AgOTf as the catalyst.

Yu et al. [38] established a straightforward approach for synthesizing 4-chalcogenylated pyrazoles **102** via electrophilic chalcogenation and cyclization of α,β-alkynic hydrazones **100**. The cyclization of α,β-alkynic aldehyde hydrazones could be triggered by employing either sulfenyl chloride or the in situ-generated S-electrophiles from the reaction of NCS and arythiol **101** (see Scheme 32). This innovative method was effectively utilized in the synthesis of the sulfenyl analogue of celecoxib, demonstrating its versatility and potential for accessing valuable chalcogenylated pyrazole derivatives.



R_1 = Ph, 4-MePh, 4-OMePh, 3-thiothenyl, ^{t}Bu
R_2 = Ph, 4-NO_2Ph
R_3 = Ph, 4-MePh, 4-OMePh, 4-NO_2Ph

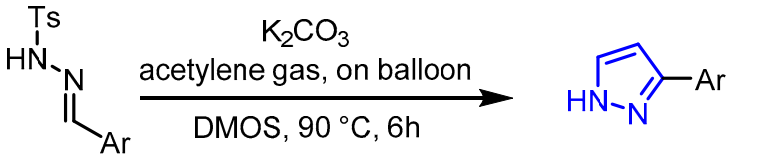
Reaction condition A: **100** (0.1 mmol), **101** (0.15 mmol), $AlCl_3$ (0.1 mmol) in $MeNO_2$ (2 mL) at 60 °C for 4–6 h.
Reaction condition B: NCS (0.15 mmol) and arylthiol (0.15 mmol), $MeNO_2$ (1 mL), RT, 0.5 h, and then 1 (0.1 mmol) and $AlCl_3$ (0.1 mmol) in $MeNO_2$ (1 mL) were added.
Benzeneselenenyl chloride (0.15 mmol) was used.

Scheme 32. The synthetic route for pyrazoles **102**.

2.2. Dipolar Cycloadditions

2.2.1. Pyrazoles from Diazo Compounds

Li et al. [39] conducted an investigation on the 1,3-dipolar cycloaddition of *N*-tosylhydrazones **103** with acetylene gas using a balloon setup. Throughout the study, various bases and solvents were tested, and K_2CO_3 was identified as the most efficient base to facilitate this reaction. When dealing with *N*-tosylhydrazones derived from aldehydes, DMSO yielded superior results, whereas NMP proved to be a more appropriate solvent for the reaction of ketone *N*-tosylhydrazones. As a result of their work, Li and colleagues successfully provided a series of pyrazoles **104** in moderate to good yields (see Scheme 33). This practical approach is easy to handle and holds promise for potential industrial applications.

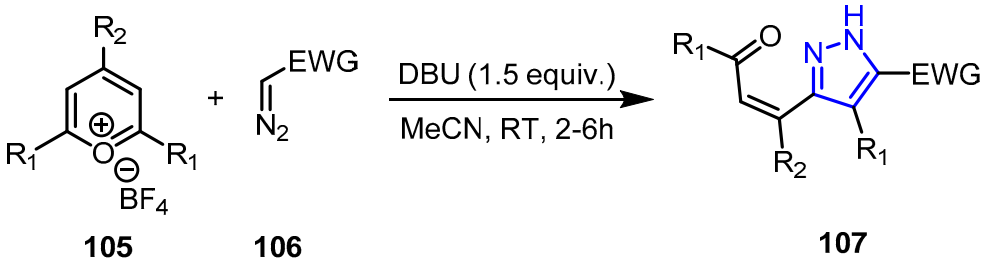


Ar = Ph, 4-MePh, 3-MePh, 2-MePh, 4-NMe_2Ph,
2-OMePh, 4-OMePh, 4-CF_3Ph, 4-BrPh, 3-BrPh

Scheme 33. The synthetic route for pyrazoles **104**.

Devi and his colleagues devised a novel approach involving a formal 1,3-dipolar cycloaddition of α-diazo phosphonates, sulfones, and trifluoromethanes **106** with 2,4,6-trisubstituted pyrylium tetrafluoroborate salts **105** [40]. This innovative approach led to the synthesis of functionalized pyrazole-chalcones **107** (see Scheme 34). The reaction proceeds via an initial nucleophilic addition of diazo substrates to pyrylium salts, followed by a base-

mediated pyrylium ring-opening and intramolecular 1,5-cyclization, resulting in formal 1,3-dipolar cycloaddition products. Afterward, the products underwent a Nazarov-type cyclization upon hydride reduction, followed by acidic workup, leading to the formation of the corresponding indenyl-pyrazoles in high yields. This methodology presents a promising strategy for the efficient synthesis of functionalized pyrazole-chalcones and indenyl-pyrazoles with potential applications in various fields.



105 **106** **107**

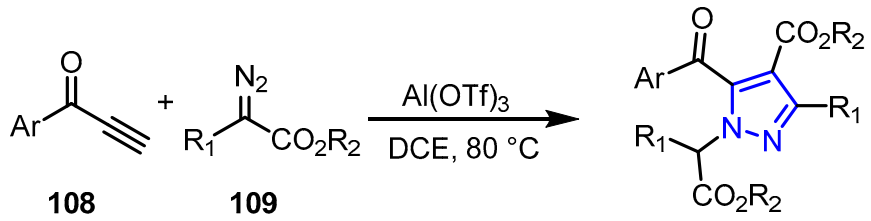
EWG: SO_2Ph, Tosyl, CF_3

R_1 = Ph, 4-OMePh, 4-MePh, 4-ClPh

R_2 = Ph, 4-OMePh, 4-MePh, 3-OMePh, 3-ClPh

Scheme 34. The synthetic route for pyrazoles **107**.

Zhao et al. [41] presented a comprehensive study on cascade reactions involving alkyl α-diazoesters and ynones with $Al(OTf)_3$ as the catalyst. Through a sequence of [3 + 2] cycloaddition, 1,5-ester shift, 1,3-H shift, and N-H insertion processes, a series of 4-substituted pyrazoles **110** were successfully synthesized (see Scheme 35). To gain insights into the mechanism, the researchers conducted deuterium labelling experiments, kinetic studies, and control experiments, which provided valuable information for rationalizing the reaction pathways and understanding the underlying mechanisms involved.



108 **109** **110** (14–64%)

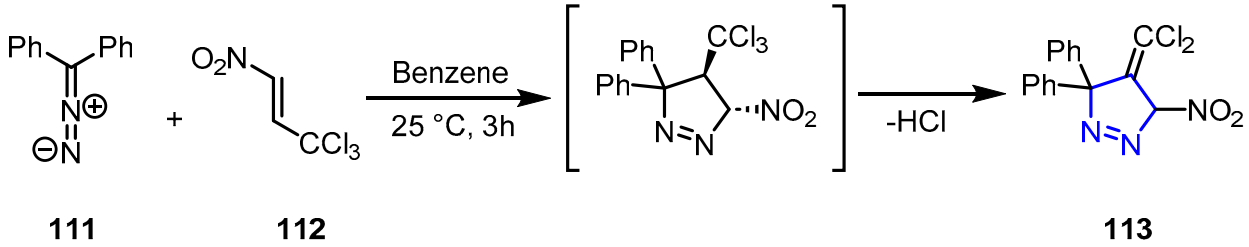
R_1 = Me, Ph

R_2 = Me, Et

Ar = Ph, 4-FPh, 4-MePh, 4-ClPh, 4-BrPh, 4-CF_3Ph, CO_2MePh

Scheme 35. The synthetic route for pyrazoles **110** using $Al(OTf)_3$ as the catalyst.

In 2021, Kula and colleagues introduced an innovative investigation into pyrazole synthesis and properties. Their work encompassed both experimental and theoretical studies on the thermal decomposition of 3,3-diphenyl-4-(trichloromethyl)-5-nitropyrazoline **113** [42]. Additionally, they explored the [3 + 2] cycloaddition reaction between diphenyldiazomethane **111** and (*E*)-3,3,3-trichloro-1-nitroprop-1-ene **112**, resulting in the synthesis of 3,3-diphenyl-4-(dichloromethylene)-5-nitropyrazoline at room temperature (see Scheme 36). This reaction serves as a notable instance of methylene-functionalized pyrazole derivatives.

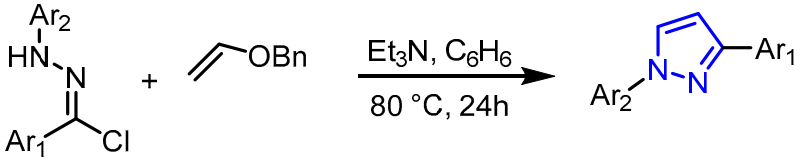


111 **112** **113**

Scheme 36. The synthetic route for pyrazole **113**.

2.2.2. Pyrazoles from Nitrilimines

In a notable contribution, Ledovskaya and her team discovered that the mild organic base trimethylamine (TEA) effectively facilitated the 1,3-dipolar cycloaddition of vinyl ethers **115** and hydrazonoyl chlorides **114**, leading to the formation of 1,3-disubstituted pyrazoles **116** with absolute regioselectivity [43] (as shown Scheme 37).

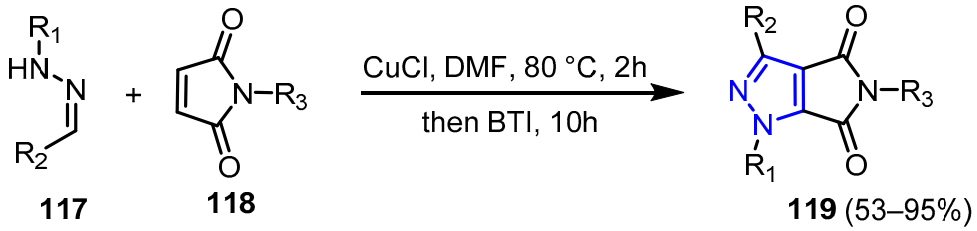


114 **115** **116** (77–99%)

Ar_1 = Ph, 4-MePh, 4-OMePh
Ar_2 = Ph, 4-MePh, 4-BrPh, 4-FPh

Scheme 37. Pyrazoles **116** synthesized via 1,3-dipolar cycloaddition with TEA promoter.

In another study, Zhu et al. [44] presented a study involving a CuCl-catalyzed oxidative coupling reaction between aldehyde hydrazones **117** and maleimides **118**, which enables the synthesis of dihydropyrazoles **119** under mild conditions. Employing this method, a diverse range of pyrrolo[3,4-c]pyrazoles was readily accessible from dihydropyrazoles using a one-step oxidation process (as depicted in Scheme 38).

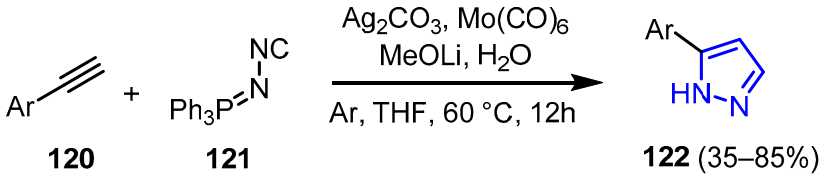


117 **118** **119** (53–95%)

R_1= Aryl, Alkyl
R_2= CO_2Et, CHO, PhCO
R_3= H, Me, Ph, Bn

Scheme 38. Synthesis of pyrrolopyrazoles **119** using Cu(I)-catalyzed cycloaddition.

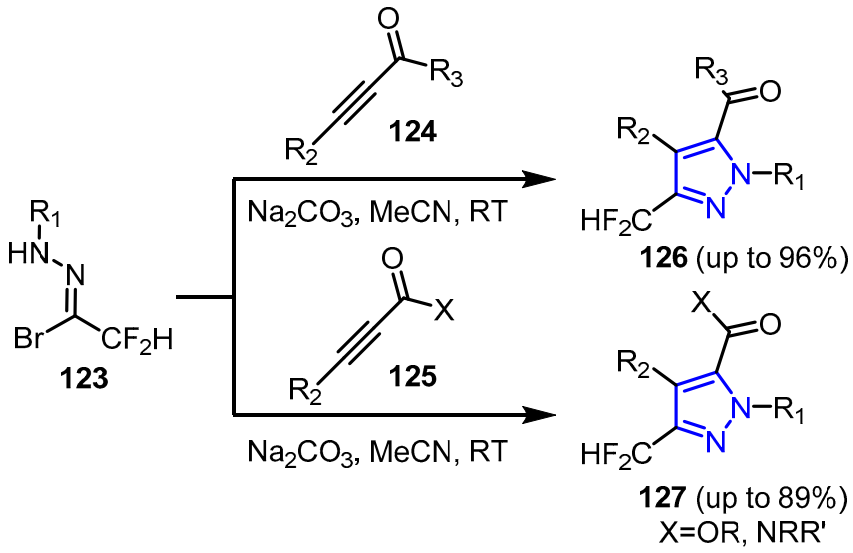
Yi and colleagues introduced an innovative approach involving a silver-mediated [3 + 2] cycloaddition of alkynes and N-isocyanoiminotriphenylphosphorane (NIITP) to construct monosubstituted pyrazoles [45]. This reaction occurs under mild conditions, exhibiting a wide substrate scope and excellent tolerance towards various functional groups. Mechanistic investigations revealed that NIITP is activated by $Mo(CO)_6$, subsequently engaging in a [3 + 2] cycloaddition with a silver acetylide intermediate (as shown in Scheme 39).



Ar = Ph, 2-OMePh, 3-MePh, 3-OMePh, 3-NH_2Ph, 3-FPh, 4-^{t}BuPh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 4-CNPh, 4-AcPh, 4-PhPh, 3-Me,4-OMePh, 2-Pyridinyl, 3-Thiophenyl, Naphthyl, 2-(benzo[*d*][1,3]dioxol-5-yl)

Scheme 39. Synthesis of pyrazoles **122** using Ag(II)-catalyzed cycloaddition.

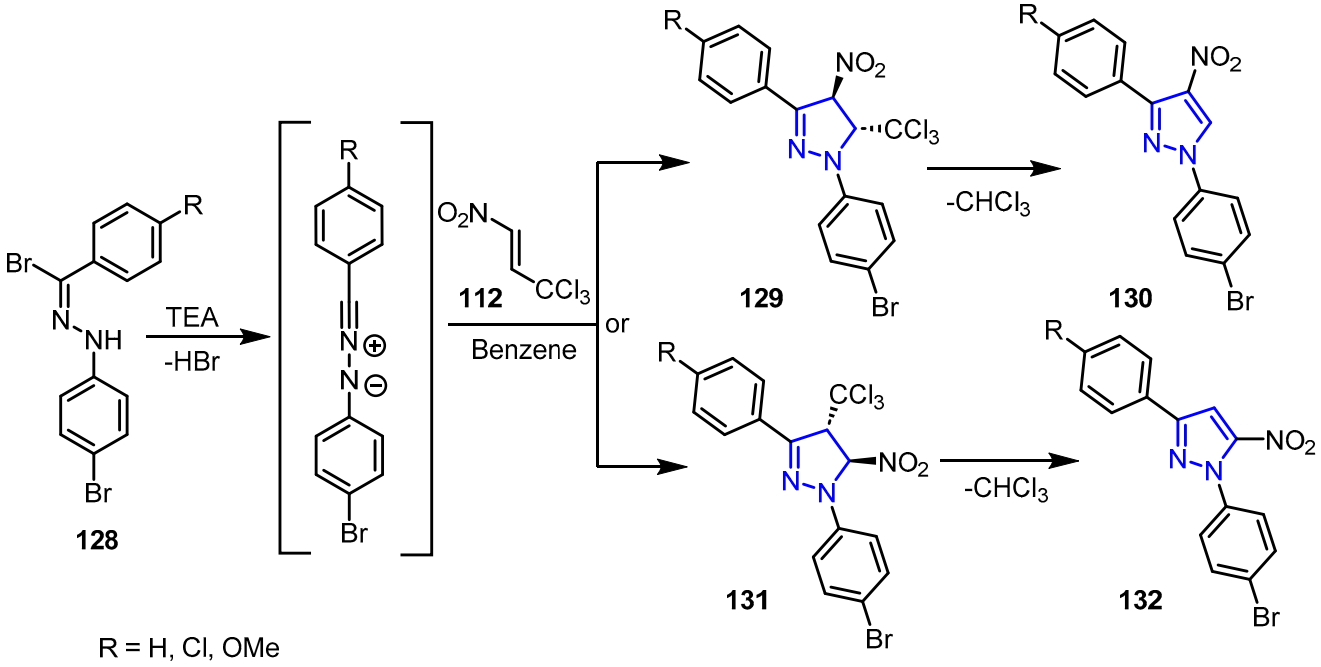
For the first time, Han and his team successfully synthesized a novel and efficient difluoromethyl building block, namely difluoroacetohydrazonoyl bromides [46]. Demonstrating its synthetic versatility, this reagent enables the construction of difluoromethyl organic compounds via effective regioselective [3 + 2] cycloaddition reactions with ynones, alkynoates, and ynamides. These reactions offer a novel and efficient protocol to access difluoromethyl-substituted pyrazoles **126** and **127** with high yields, representing a significant advancement in difluoromethyl chemistry (as shown in Scheme 40).



R_1 = Ph, 2-MePh, 3-MePh, 4-MePh, 4-EtPh, 4-^{t}BuPh, 4-BrPh, 4-FPh, 4-CF_3Ph, Naphthyl
R_2 = H, CO_2Me
R_3 = Ph, 2-MePh, 3-MePh, 4-MePh, 2-FPh, 3- FPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, Naphthyl, 2-Thiophenyl, 2-Furanyl, Cyclohexyl, Penthyl, Me, ^{t}Bu, OMe, O^{t}Bu, OPh, 4-MePhO, 4-ClPhO, *N*-PhNH, *N*-4-MePhNH, *N*-4-ClPhNH, *N,N*-Me,PhN, *N,N*-Me,OMeN, *N,N*-diMeN

Scheme 40. Synthetic routes for pyrazoles **126** and **127**.

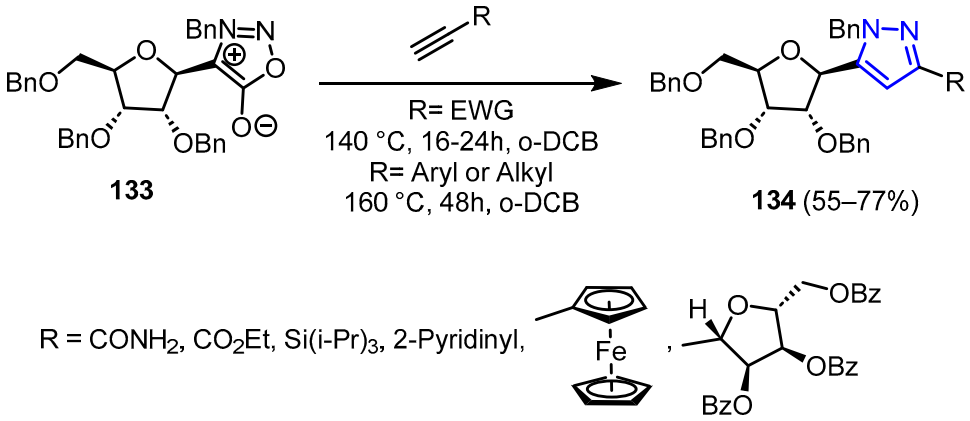
Kula et al. [47] in 2022 explored the experimental and theoretical studies on the reaction between (*E*)-3,3,3-trichloro-1-nitroprop-1-ene **112** and N-(4-bromophenyl)-C-arylnitrylimine **128**. The title process led to the formation of the corresponding pyrazoles **130** and **132** (see Scheme 41).



Scheme 41. Synthetic routes for pyrazoles **130** and **132**.

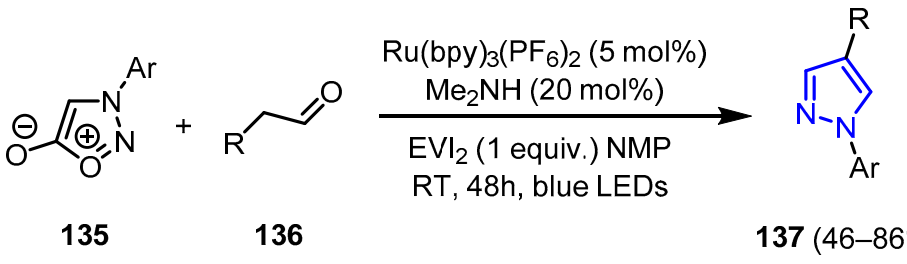
2.2.3. Pyrazoles from Sydnones

Bouton et al. [48] successfully synthesized the C-nucleoside natural products, formycin B, and pyrazofurin **134**, in seven steps, utilizing a sydnone riboside **133** as a shared intermediate. The sydnone ribosides were created using a direct Lewis acid-catalyzed dehydrative glycosylation reaction. It was demonstrated that these intermediates could be employed for the diversity-oriented synthesis of pyrazole C-nucleoside analogues via thermal 1,3-dipolar cycloaddition reactions with various alkynes (as shown in Scheme 42). This approach not only provided access to the pyrazole C-nucleoside natural products but also opened up new possibilities for exploring the chemical space of nucleosides.



Scheme 42. The [3 + 2] Cycloadditions of Sydnone Riboside **133** with Different Alkynes.

Lakeland and his research team reported a regioselective reaction achieved via a visible-light photoredox process, employing $Ru(bpy)_3(PF_6)_2$ as the catalyst [49] (as depicted in Scheme 43). This innovative approach enabled the synthesis of a wide range of 1,4-disubstituted pyrazoles **137** with excellent yields.

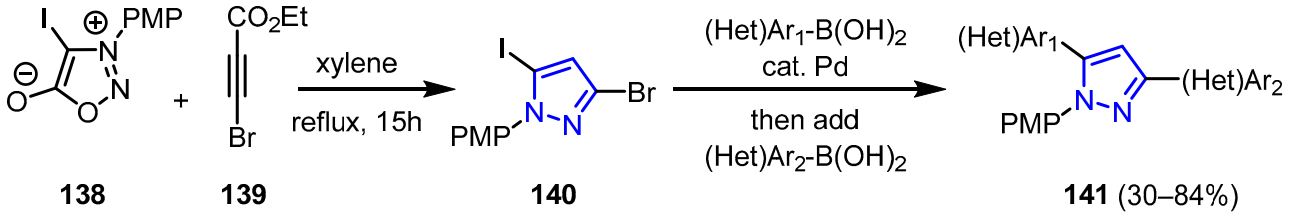


135 **136** **137** (46–86%)

Ar = H, 4-OMePh, 4-CNPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 3-MePh
R = Buthyl, iPr, Cyclohexyl, Me, Ph, Benzyl, TBSO-Buthyl, $(CH_2)_2CO_2Me$, $(CH_2)_2CO_2Me$, $(CH_2)_2CO_2N(OMe)Me$

Scheme 43. Synthesis of pyrazoles **137** using Ru(II)-catalyzed photoredox cycloaddition.

Delaunay et al. [50] presented a significant research study on the [3 + 2] dipolar cycloaddition of 4-halosydnones with 1-haloalkynes, offering a straightforward route to access 3,5-dihalopyrazoles. These dihalopyrazoles serve as valuable scaffolds for generating unsymmetrically 3,5-substituted pyrazole derivatives via site-selective Pd-catalyzed cross-coupling reactions. For instance, they demonstrated the flexible introduction of different (hetero)aryl substituents at the C-5 and C-3 positions of the PMP-protected pyrazole nucleus in a one-pot operation, utilizing sequential reactions with various boronic acids (as depicted in Scheme 44). This method offers a versatile strategy for the synthesis of diverse pyrazole derivatives.



138 **139** **140** **141** (30–84%)

Ar_1 = 4-FPh, 4-AcPh, 3-Pyridinyl, 2-Furanyl, 2-Thiophenyl, 2-(benzo[*d*][1,3]dioxol-5-yl)
Ar_2 = 3-Pyridinyl, 4-Pyridinyl, 2-Furanyl, 2-Thiophenyl, CO_2MePh, 4-ClPh, 3-CF_3Ph

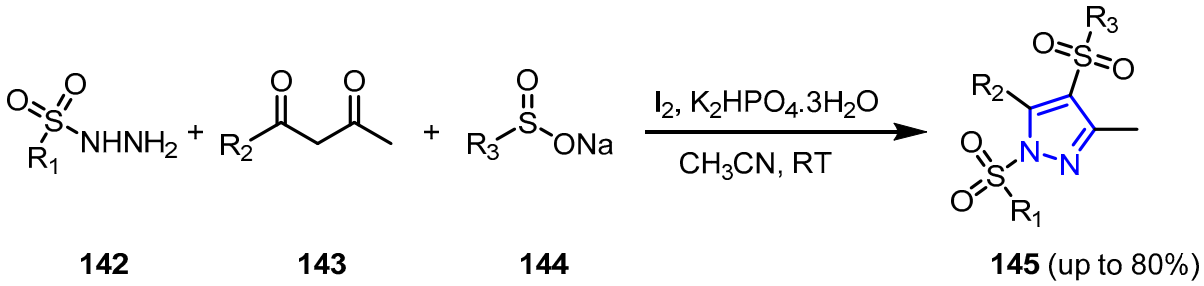
Scheme 44. The synthetic route for pyrazoles **141**.

2.3. Multicomponent Synthesis

Multicomponent Synthesis (MCS) is a powerful and innovative strategy in organic chemistry that has revolutionized the field of chemical synthesis. It is a method of constructing complex molecules by combining multiple starting materials in a single reaction step. This approach contrasts with traditional organic synthesis, which often involves sequential reactions and the use of protecting groups, leading to increased steps and waste generation.

Among the numerous significant studies mentioned in the literature, Chen et al. [51] introduced a transition metal-free method utilizing molecular iodine as a catalyst to synthesize sulfonated pyrazoles from sulfonyl hydrazides, 1,3-diketones, and sodium sulfinates under mild conditions. This innovative approach enabled the direct one-step formation of pyrazoles with two distinct sulfonyl groups. Through control experiments, the reaction described in [51] was elucidated, and a plausible mechanism was attributed to it. The process involves the facile generation of sulfonyl iodide by the interaction of sodium sulfinate **144** and molecular iodine. Subsequently, the condensation of sulfonyl hydrazides **142** and 1,3-diketones **143** forms an imine, which undergoes tautomerization to yield its enol form.

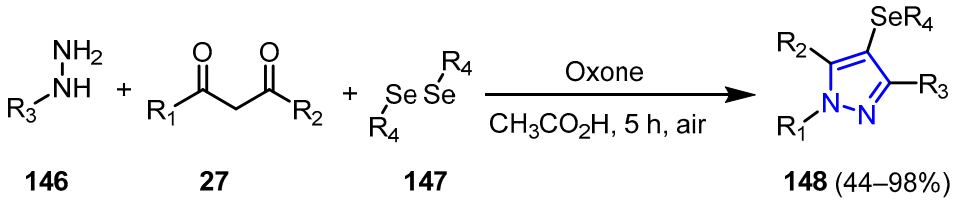
An in situ generated sulfonyl iodide, derived from the enol form, undergoes nucleophilic attack leading to an intermediate, ultimately resulting in the desired products **145** via an intramolecular condensation (as depicted in Scheme 45).



R_1 = Ph, 4-MePh, 4-PhPh, Naphthyl, 4-^{t}BuPh, 3-MePh, 4-OMePh, 4-FPh, 4-BrPh, 4-ClPh, 4-IPh,
R_2 = Me, ^{t}Bu, n-C_5H_{11}, Ph, 4-MePh, 4-OMePh, Naphthyl, 4-FPh, 4-ClPh, 4-BrPh, 3-ClPh, 3-Thiophenyl, 2-Furanyl, 2-Pyridinyl
R_3 = Ts, PhO_2S

Scheme 45. Synthesis of sulfonated pyrazoles **145** via transition metal-free method, using molecular iodine as a catalyst.

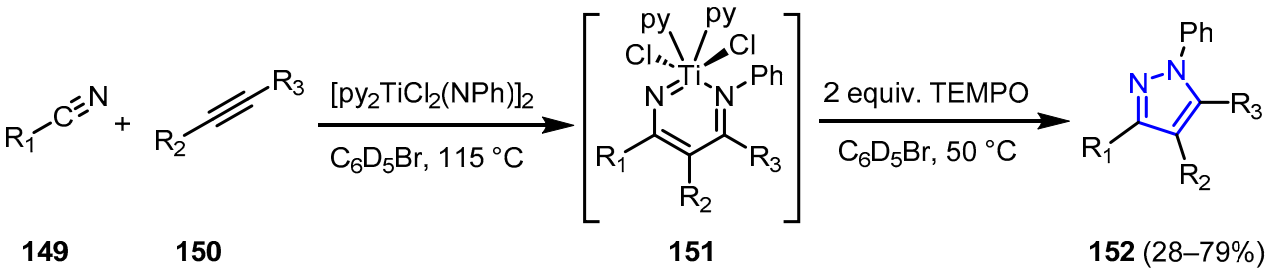
In another study, Jacob and colleagues presented an exceptionally efficient one-pot procedure to synthesize 4-organylselanylpyrazoles **148** by means of direct cyclocondensation and C-H bond selenylation reactions. This method commences with hydrazines **146**, 1,3-diketones **27**, and diorganyl diselenides **147**, employing Oxone as the promoting agent. The products were obtained using a metal catalyst-free approach, operating under mild conditions, leading to short reaction times, and yielding products in moderate to excellent yields [52] (see Scheme 46).



R_1 = Me, Et, Ph
R_2 = Me, Et
R_3 = H, Ph, 2,4-diMePh, 2,4-diClPh
R_4 = Ph, 4-MePh, 4-OMePh, 4-ClPh, 4-FPh, Buthyl, 2-Pyridinyl

Scheme 46. Oxone promoted the synthesis of 4-organylselanylpyrazoles **148**.

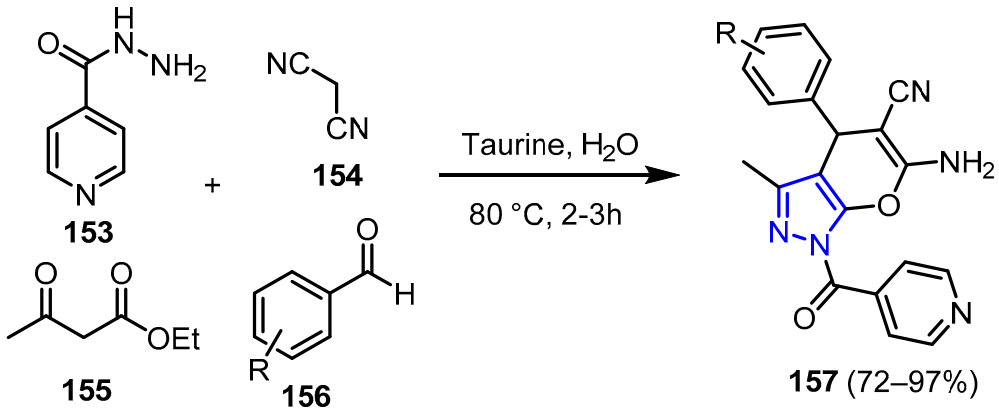
A recent groundbreaking contribution by Pearce and colleagues introduced a novel fragment combination mode [NC] + [CC] + [N] utilizing a multicomponent oxidative coupling to synthesize multi-substituted pyrazoles. These innovative reactions involved the formation of diazatitana-cyclohexadiene intermediates by combining alkynes, nitriles, and titanium imido complexes, leading to pyrazole derivatives **152** via a 2-electron oxidation process catalyzed by the oxidant TEMPO [53] (see Scheme 47).



R_1 = Ph, 4-Me-Ph, 4-MeOPh, 4-CF_3-Ph, iPr, Me
R_2 = Me, Et, Ph, 4-^{t}BuPh
R_3 = Me, Et, 4-^{t}BuPh

Scheme 47. Organotitanium promoted the synthesis of pyrazoles **152**.

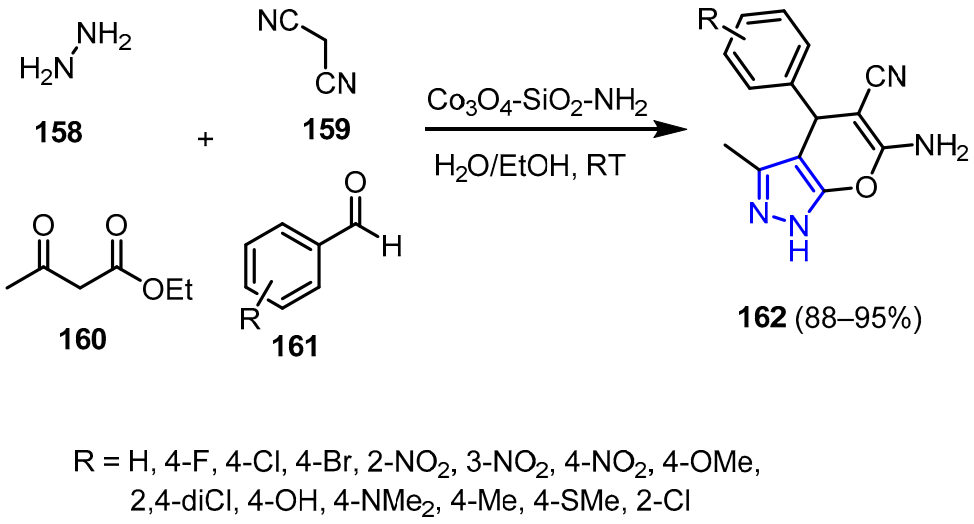
In 2021, Mali and colleagues introduced an efficient and environmentally friendly multicomponent approach, catalyzed by taurine, for the synthesis of densely substituted therapeutic core dihydropyrano[2,3-*c*]pyrazoles **157** [54] (see Scheme 48). This pioneering method enabled the synthesis of a diverse array of 1,4-dihydropyrano[2,3-*c*]pyrazoles, incorporating isonicotinamide, spirooxindole, and indole moieties. The application of these synthetic strategies and technologies led to the creation of novel compounds.



R = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 2,6-diCl,
4-OH, (3-OMe,4-OH), 3,4,5-triOMe

Scheme 48. Green Multicomponent Approach for the Synthesis of pyrazoles **157**.

In another study, Shahbazi and collaborators successfully prepared a range of pyranopyrazoles **162** using a convenient one-pot four-component reaction involving ethyl acetoacetate **160**, hydrazine hydrate **158**, aldehydes **161**, and malononitrile **159**. They employed Co_3O_4-SiO_2-NH_2 nanocomposites as the catalyst in this process [55] (see Scheme 49). The study highlights numerous benefits, such as remarkably short reaction times, outstanding yields, an environmentally friendly approach, straightforward purification methods, and the economical accessibility of the catalyst.



Scheme 49. Synthesis of pyranopyrazoles **162** by one-pot cyclization using Co_3O_4-SiO_2-NH_2 nanocomposites as a catalyst.

3. Conclusions

Pyrazoles constitute a class of five-membered heterocyclic compounds that contain two nitrogen atoms. They play a crucial role in drug development, acting as essential hit compounds for designing innovative pharmacological agents to target a variety of clinically significant infections. The extensive pharmaceutical applications of pyrazoles have driven swift progress in pyrazole synthesis methodologies. In the last decade, numerous effective and versatile approaches have arisen, encompassing the use of transition-metal catalysts and photoredox reactions, as well as one-pot multicomponent processes, novel reactants, and innovative reaction modalities. These developments have significantly contributed to the synthesis and functionalization of pyrazole derivatives. The comprehensive information presented in this review will prove valuable for aspiring researchers looking to delve into the world of pyrazole derivatives. By gaining insights from this review, researchers can explore the possibility of other derivatizations to expand the repertoire of pyrazole-based compounds. However, there is still room for further investigation, especially in cases where the pyrazole unit itself plays a pivotal role in the compound's mode of action, as well as situations where the pyrazole serves more as a structural element. These aspects warrant further exploration to fully comprehend the diverse potential and applications of pyrazole derivatives. Nevertheless, these reactions have the potential to provide very interesting molecular structures. In view of the growing importance of pyrazoles, we believe that the development of new synthetic routes using condensations, cycloadditions, and other potential methods will enhance our understanding of this field in the future.

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