PYRAZOLE: SYNTHESIS, REACTION AND BIOLOGICAL ACTIVITY

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ABSTRACT

This review summarizes the synthetic methods, reactions and biological application of pyrazole and summarizes recent developments in their derivatives such as formyl pyrazole, Schiff base, chalcone, Aromatic nucleophilic substitution etc. over the last 10 years. Formation of Pyrazole and fused heterocyclic pyrazole derivatives constitute an interesting class of heterocycles, which have diverse biological activities. The biological activity of the pyrazole is also briefly discussed.

KEYWORDS: Pyrazole, biological activity, Pyrazolopyridine heterocycle, Schiff base, chalcone.

INTRODUCTION

Pyrazole belongs to the “diazole” class of heterocycles and is the most important moiety found in a large number of pharmaceutical agents. Substituted pyrazoles are important compounds of many drugs and drug candidates. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Due to the pyrazole moiety & unique in their chemical behaviour. A diversity of biological activities and pharmaceutical uses have been attributed to them, such as pyrazole is a part of many active molecules possessing activities such as anti-tubercular,[¹] anticancer,[²] antiviral,[³,⁴] antibacterial,[⁵] antifungal,[⁶] anti-inflammatory,[⁷,⁸] antimicrobial,[⁸,⁹] Antidepressant,[¹⁰] anticonvulsant,[¹⁰] in vivo anti-inflammatory,[¹¹] in vitro antioxidant,[⁸] analgesic,[⁷] anti-angiogenic. [¹²] The substituted
pyrazole moiety 1 appears as an interesting precursor of many biologically active of the above class compounds.

This review provides an overview of the synthesis and reactivity of pyrazole and derivatives. In first part we intend to outline the general methods by which substituted pyrazole are prepared. The second and third parts are devoted to the chemical reactivity of substituted pyrazoles.

1. Synthetic Methods
There have been a number of practically important routes to synthesize Pyrazoles.

2.1 Oxaziridine Mediated One Pot Synthesis of Pyrazole
A well-established route for synthesis of substituted pyrazole 3 was reported by one pot electrophilic amination of amines 2 using N-Boc-oxaziridine, NaHCO₃, MgSO₄, & 1,3 dicarbonyl compounds (Scheme 1). [13]

2.2 Palladium Catalyzed Synthesis of Pyrazole
Synthesis of substituted pyrazole 8 was reported by four component coupling reaction using phenylethyne 4, aqueous hydrazine 5, carbon monoxide 6, and iodobenzene 7 in the presence of PdCl₂(PPh₃)₂ in THF (Scheme 2). [14]
2.3 Rapid One Pot Synthesis of Pyrazole

Rapid one pot synthesis of pyrazole 13 is studied & reported that formation of 1,3 diketones 11, takes place directly from ketones 9, and acid chlorides 10 in basic medium, and were then converted in situ into pyrazoles by the addition of hydrazine 12 (Scheme 3).[15]

2.4 Synthesis of Pyrazole Using N-Substituted Hydrazone and Nitroolefins

One pot Regioselective synthesis of substituted pyrazoles 17 was reported by using N-monosubstituted hydrazones 14, and nitroolefins 15 via nitropyrazolidine 16 as a intermediate in presence of methanol & water. (Scheme 4).[16]
2.5 Synthesis of Fluorinated Pyrazole from Benzoylfluoroacetonitrile & Hydrazine

Benzoylfluoroacetonitrile 18 underwent cyclisation with hydrazine hydrate in isopropyl alcohol to give fluorinated pyrazole 19. (Scheme 5). \[17\]

\[
\begin{array}{c}
\text{18} \\
\text{F} \\
\text{CN} \\
\text{1 equiv. } \text{NH}_2\text{NH}_2 \\
(80 \% \text{ in } \text{H}_2\text{O}) \\
i-\text{PrOH}, \Delta, 0.5 \text{ h} \\
\text{19}
\end{array}
\]

Scheme 5

2.6 Synthesis from Hydrazones of β- Keto Esters

The new protocol developed for the synthesis of pyrazole 21 from Hydrazones of β- keto esters 20 using DMF-POCl₃ on reflux. (Scheme 6). \[18\]

\[
\begin{array}{c}
\text{20} \\
\text{R}_1\text{COOCH}_2\text{R}_2 \\
\text{NO}_2 \\
\text{DMF-POCl}_3 \\
i) \text{ reflux, } 4 \text{ h} \\
\text{21}
\end{array}
\]

Scheme 6

2.7 Microwave Assisted Synthesis of Pyrazole on SiO₂ Support

The new method for synthesis of pyrazole 23 was reported by, using Hydrazones of β- keto esters 22 undergo microwave irradiation gives good yield in short time, better yields are obtained upon microwave irradiation of the reaction mixture on SiO₂ support (Scheme 7). \[18\]

\[
\begin{array}{c}
\text{22} \\
\text{R}_1\text{COOCH}_2\text{R}_2 \\
\text{NO}_2 \\
\text{ii) MWI , or} \\
\text{iii) SiO}_2 / \text{MWI} \\
\text{23}
\end{array}
\]

Scheme 7
2.8 Synthesis from B- Diketone Using Claisen Condensation Reaction

Reactions were studied and reported the synthesis of substituted pyrazole 27 by condensation of methyl 2-(hydroxymethyl) picolinate 24 & acetyl pyridine 25 in NaOC2H5, forms β-diketone 26 which on reflux with hydrazine hydrate in ethyl alcohol (Scheme 8).

![Scheme 8]

2.9 Synthesis of N-Arylsulfonyl Pyrazoles from Arylsulfonyl Hydrazone

N-arylsulfonyl pyrazoles 30 have been synthesized by the multicomponent reaction of arylsulfonyl hydrazones 28 and dialkyl acetylenedicarboxylates 29 in the presence nucleophilic compounds such as pyridine, isoquinoline, or triphenylphosphine using CH2Cl2 (Scheme 9).

![Scheme 9]

2.10 Synthesis of Substituted Pyrazole from Chalcone And P-Sulfamylphenyl Hydrazine

A convenient route for the synthesis of pyrazole is reported by α,β-unsaturated ketones 33 is achieved by base catalyzed condensation of benzyl methyl ketone 32 with the appropriate p-substituted benzaldehyde 31 in the presence of piperidine, which reacts with p-
Scheme 10

sulfamylphenyl hydrazine gives hydrazone 34. The hydrazone mixture reflux with 30% HCl gives pyrazole 35 which shows more significant antimicrobial activity. (Scheme10).[21]

2.11 Microwave Assisted Synthesis of 4, 5- Dihydro-pyrazole Using Hydrazine Derivative with alkyl dihalides in aq. Media

Microwave assisted synthesis of 4,5-dihydro-pyrazole 38 was reported by cyclocondensation of hydrazine derivative 36 with alkyl dihalides 37 in aq.media (Scheme11).[22]

Scheme 11

2.12 Synthesis of Pyrazoles Using Acid Chlorides, Terminal Alkynes, and Hydrazines

The reaction of acid chloride 39 with terminal alkynes 40 and hydrazine 41 in presence of PdCl₂ (PPh)₃ / CuI, Et₃N, THF gave the afforded three component synthesis of Pyrazole 42 (Scheme 12).[23]
2.13 One Pot Synthesis of Pyrazole from B-Formyl Enamides
A novel one-pot synthesis of pyrazoles 45 has been accomplished by the reaction of β-formyl enamides 43 with hydroxylamine hydrochloride forms oxime intermediate 44 catalysed by potassium dihydrogen phosphate in acid medium (Scheme 13).\textsuperscript{[24]}

Scheme 13

2.14 Microwave-Promoted Solvent Free Synthesis of Optically Active Pyrazoles
Microwave-promoted solvent free synthesis of optically active pyrazoles 47 was reported by using 2-Formyl glycals 46 undergo rapid condensation with arylhydrazines gives optically pure 4-substituted pyrazoles (Scheme 14).\textsuperscript{[25]}

Scheme 14

2.15 One-Pot Preparation of 3, 5- Disubstituted Pyrazoles
One-pot preparation of 3, 5-disubstituted pyrazoles 49 was reported by using terminal alkynes 48 aldehydes, molecular iodine, and hydrazines (Scheme 15).\textsuperscript{[26]}
2.16 Fe- Catalyzed one Pot Synthesis of Substituted Pyrazole

Fe-catalyzed one-pot regioselective synthesis of 1, 3- and 1, 3, 4-substituted pyrazoles was reported by reaction mixture of diarylhydrazones and vicinal diols. The mixture was stirred under O2 atmosphere at RT. To the resulting mixture acetyl acetone followed by TBHP was added dropwise and the temperature was slowly increased to 80-120°C (Scheme 16).

2.17 From 1, 3 Diketone & Phenyl Hydrazine in Mg (Hso₄)₂ Catalyst

Facial and solvent free synthesis of substituted pyrazole was reported by using 1, 3 Diketone and hydrazine in Mg (HSO₄)₂ as ecofriendly catalyst (Scheme 17).

2.18 Amberlyst-70 Catalysed Synthesis of Pyrazoles

Greener and facile aqueous synthesis of pyrazoles were reported by using acetyl acetone and phenyl hydrazine using Amberlyst-70 as a recyclable catalyst (Scheme 18).
Scheme 18

2.19 Microwave Assisted Synthesis of Substituted Pyrazole

Under microwave activation, Acetophenone 59 reacted with Substituted hydrazine 60 forms hydrazones 61. The latter compound underwent reaction with DMF/POCl₃ to give Pyrazole-4-carbaldehyde 62 which showed anti-inflammatory, analgesic and ulcerogenicity activities (Scheme 19). [30]

Scheme 19

2.20 Synthesis of Pyrazoles Using Substituted Aryl Hydrazine

Synthesis of a series of substituted pyrazoles 70 - 75 were reported by refluxing substituted Aryl hydrazine 63 with Ethoxy Methylene Malononitrile 64 Tetracyanoethylene 65 Ethyl (Ethoxymethylene) – Cyanoacetate 66 Bis (Methylthio)-Methylene malononitrile 67 acetylacetone 68 Ethylacetoacetate 69 Some of these compounds showed more Significant antimicrobial activity than some known drugs. (Scheme 20). [31]
2.21 Synthesis Using Enol Ether with Hydrazine Hydrate

Substituted pyrazoles 78 were synthesized by using activated enol ether 76 with substituted hydrazine hydrate 77 the activated enol ethers is prepared by the condensation of active methylene components such as malonic acid derivatives (esters, nitrile etc) with trialkyl orthoformate (Scheme 21). \(^{[32]}\)
2.22 Synthesis from α, β Dibromo 4, 4′ Difluorochalcone with Various Hydrazines Hydrates

Synthesis of substituted pyrazoles 81-82 were reported by using α, β dibromo 4, 4′ Difluorochalcone 80 obtained from (4, 4′ difluorochalcone 79) with various substituted hydrazines hydrate (Scheme 22).[33]

3. Chemical Reactions

3.1 Macrocyclic Schiff base Formation

The novel macrocyclic Schiff bases upon which were fused triazole and pyrazole units and containing N, O and S inside the macrocyclic ring as donor atoms 86a-r were synthesized by
condensation of bis (4-amino-1,2,4-triazole-3-yl-sulfanyl)alkanes 84 and pyrazoledialdehyde 85 in refluxing glacial acetic acid (Scheme 23).[34]

\[ \text{Scheme 23} \]

3.2 Synthesis of Pyrimidin-4-Ones Heterocycle

A Simple and rapid one pot Synthesis of 1- arylpyrazolo[3,4-d] pyrimidin-4-ones 88 using 5-amino-N-Substituted-1H-Pyrazole-4-Carbonitrile 87 and different lower aliphatic acid in presence of POCl$_3$ was reported. (Scheme 24).[35]
3.3 Synthesis of Substituted Thiophene Heterocycle

Pyrazole 89 on reaction with either malononitrile or ethyl cyanoacetate 90a-b and Elemental sulfur in presence of triethylamine as basic catalyst afforded the pyrazol-1-yl N-thiophen-5-yl derivatives 91a-b such synthesis is called as Gewald thiophene synthesis Some of these compounds exhibiting the inhibitory effects towards the three tumor cell lines Mcf-7, NCI-H460, Sf-268. (Scheme 25). \[36\]

![Scheme 25]

3.4 Nucleophilic Aromatic Substitution

The nucleophilic aromatic substitution on 5-chloropyrazoles activated by the electron-withdrawing formyl group 92 offers a useful method to introduce a wide range of N-containing heterocycles into 93. Nucleophilic substitution take place by N-containing heterocycles in presence of base KOH & DMF. (Scheme 26). \[37\]

![Scheme 26]

3.5 Synthesis of Imidazolyl-Pyrazole Heterocycle

Synthesis of Imidazolyl-Pyrazole 96 was reported by Acid-Promoted multicomponent reaction of pyrazole aldehyde 94 benzyl 95 and ammonium acetate. The reaction mass was subjected to ultra sound irradiation at room temperature for 20-40 minutes. (Scheme 27). \[38\]
3.6 Synthesis of Substituted Pyrazolopyridine Heterocycle

Pyrazolopyridine 3-Carboxylates 99 101 103 105 107 109 were synthesized by Friedlander Condensation. The novel Friedlander condensation of o-aminoaldehyde 97 with α-methylene ketones, nitriles, and esters containing active methylene groups were carried out in the presence of piperidine and ethyl alcohol. (Scheme 28).[39]
3.7 Synthesis of Novel Pyrazole Derivative

A convenient synthesis of some novel pyrazole have been reported by the reaction of 3-aryl-1-phenyl-1H- pyrazole-4- carbaldehydes 110 with some reagents such as acetylglucose, benzamidine hydrochloride, malononitrile, and ethyl azidoacetate gives the oxazolone derivative, dihydroimidazolone derivatives, pyridine derivatives, pyrrolopyrazole derivatives resp. and 3-aryl-1-phenyl-1H- pyrazole-4- carbaldehydes undergo Aldol condensation using cyclohexanone in NaOH & dimethyl sulphoxide gives α,β unsaturated compounds (Scheme 29). [40]
3.8 Miscellaneous Reactions

3.8.1 Synthesis of 3-Methyl-4-(substituted phenylhydrazono)-2-pyrazolin-5-ones

Substituted anilines 122 on diazotization using NaNO₂ / Con. HCl, at 0-5⁰C temperature gives Diazotized substituted anilines 123 were treated with Ethylacetoacetate & sodium acetate to yield ethyl-2-(substituted phenyl) hydrazono-3-oxo butyrates.124 Which on reaction with various ammonia derivatives (PhNHNH₂, NH₂NH₂ etc) in presence of glacial acetic acid forms 3-Methyl-4-(substituted phenylhydrazono)-2-pyrazolin-5-ones 125-126 these compounds exhibits the in vitro antibacterial activity. (Scheme 30).

\[\text{R}NHNH₂ + \text{PhNHNH₂, NH₂NH₂ etc} \rightarrow \text{R}NHNH₂ \rightarrow \text{R}NHNH₂ + \text{PhNHNH₂, NH₂NH₂ etc} \]

\[\text{R}NHNH₂ + \text{H}_2\text{C} = \text{COCH₃} \rightarrow \text{R}NHNH₂ + \text{PhNHNH₂, NH₂NH₂ etc} \rightarrow \text{R}NHNH₂ \rightarrow \text{R}NHNH₂ + \text{PhNHNH₂, NH₂NH₂ etc} \]

Scheme 30

3.8.2 Synthesis of 1-Hydro-5-methyl-6 (substituted phenylhydrazono)-4-pyrazolin-7-ones

Synthesis involves the treatment of ethyl acetoacetate with different diazonium salts in the presence of sodium acetate to yield ethyl-2-aryl hydrazono-3-oxo butyrates 127. The latter compounds on treatment with o-phenylenediamine furnished 1-hydro-5-methyl-6(substituted phenylhydrazono)-4-pyrazolin-7-ones 128. The compounds showed in vitro antibacterial activity. (Scheme 31).
3.8.3 Photochemistry of Substituted Pyrazoles

Photochemistry of 1-methylpyrazoles 130 involves competition between electrocyclic ring closure (Path A) and cleavage of the N1-N2 bond (Path B). Path A results in the formation of a 1,5-diazabicyclo[2.1.0] pentene intermediate, which undergoes one or two sigmatropic shifts of nitrogen followed by rearomatization of the two resulting isomeric 2,5-diazabicyclo[2.1.0] pentene species to yield 1-methylimidazoles with two different scrambling patterns identified as 131 and 132 respectively. Path B leads to a species that can be viewed as a vinyl nitrene that rearranges to a 1-methylimidazole with a 133 scrambling pattern. (Scheme 32). [43]
CONCLUSION

Pyrazoles are easily available and have high chemical reactivity a series of heterocyclic compounds containing a five membered ring consisting of three carbon atoms united to nitrogen atom thus the derivative are oriented from the imino group, the second position being at the other nitrogen atom This survey is attempted to summarize the synthetic methods and reactions of Pyrazoles during last years.

REFERENCE


34. Chen F, Liu F-M. (Synthesis of New Macrocyclic Schiff Bases Containing Pyrazole and Triazole as Subcyclic Units). J. Heterocyclic Chem, 2014; 00: 00.


