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A Mini-Review 5-Amino-N-Substituted Pyrazoles as Building Blocks for Bioactive Molecules

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Abstract

In this review a five-membered heterocyclic ring having two adjacent nitrogen atoms known as Pyrazole, we have framed 5-amino-*N*-substituted pyrazoles in particular focusing on its substantial role as a building block and starting materials for producing enormous heterocyclic skeletons. The existence of this moiety in larger compounds renders them to expose medicinal, pharmacological and biological therapeutic activities. Enormous drugs contain 5-amino-N-substituted pyrazoles such as celecoxib anti-inflammatory, antipsychotic, anti-obesity, analgesic, and antidepressant. We reported various routes of synthesis and the use of these compounds.

Keywords

Synthesis, 1,5-Disubstituted Pyrazoles, Bioactive, Review

1. Introduction

Synthesis of heterocyclic compounds is of critical importance due to their fundamental role in pharmaceutical applications. Pyrazoles and their derivatives are an important category of heterocyclic compounds that has gained significant attention recently among pharmacological, medicinal, and biological chemists. Most pyrazole derivatives exhibit significant anticancer properties [1] [2] [3] [4].

Functionally, pyrazoles are used as the starting materials or building blocks of other heterocyclic nitrogen systems such as imidazole pyrazoles [5] and pyrazolyl-1,2,4-triazines [6]. Some amino-pyrazolones such as 4-aminoantipyrine are used, for instance, as agrochemicals [7] in dyestuffs [8] as antipyretics [9], and as α-aminophosphonic acids [10].

This review reports several routes of synthesis of various 5-amino-N-substituted

pyrazole derivatives and highlights their behavior toward electrophilic and nucleophilic reagents, to which their highly active biological and pharmaceutical characteristics are due.

2. Synthesis of 5-Amino-N-Substituted Pyrazoles

Treatment of 2-hydrazino-1-phenylethanol **1** with ethyl (ethoxymethylene) cyanoacetate **2** in dry toluene at 80˚C for 8 h produces ethyl 5-amino-1-(2-hydroxy-2-phenylethyl)-1H-pyrazole-4-carboxylate **3** (Scheme 1) [11].

The condensation of hydrazine acetaldehyde diethylacetate 4 with ethyl (ethoxymethylene) cyanoacetate **2** produces 5-amino-1-(2,2-diethoxyethyl)-1N-pyrazole-4-carboxylate **5** (Scheme 2) [12].

Treatment of compound **2** with (ethoxy methylene) malononitrile **6** yields 5-amino-1-(2,2-diethoxyethyl)-1H-pyrazole-4-carbonitrile 7 (Scheme 3) [13].

Treatment of hydrazine derivatives **2** with ethyl cyano pyruvate **8** in a biphasic water/chloroform solvent in the presence of sulfuric acid results in ethyl 5-amino-1-(2,2-diethoxyethyl-1H-pyrazole-3-carboxylate **9** (Scheme 4) [14].

3-Amino-5-phenylpyrazole **11** is obtained from reaction of benzoic acid hydrazide with chloroacetonitrile (Scheme 5) [15].

3. Behaviour of 5-Amino-1-Substituted Pyrazoles towards Electrophilic and Nucleophilic Reagents

Treatment of most 5-amino-1-substituted pyrazoles with electrophilic or nucleophilic reagents led to direct formation of imidazole pyrazoles, which are candidates for considerably highly bioactive systems.

Thus, formylation of amino-1-(2-hydroxyethyl)pyrazole **12**, when treated with Ac2O–HCOOH, followed by cyclisation with NaH, produced 1-formyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazole 13 (Scheme 6) [16].

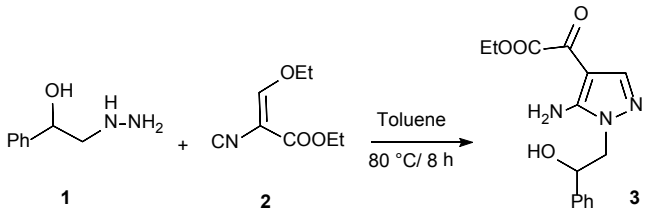
The aza-Wittig reaction of 5-amino-3-phenyl-1H-pyrazole **11** via $P(Ph)_3/C_2Cl_6/Et_3N$ at reflux with benzene produces 5-(triphenyl phosphoranylideneamino)-3-phenylpyrazole **14**, which upon treatment with *P*-chloroketone yields imidazo[1,2-b]pyrazoles 15 (Scheme 7) [17].

Dehydration of aminopyrazole **3** by treatment with concentrated H2SO4 at room temperature produces ethyl 2-phenyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazole-6-carboxylate 16 (Scheme 8) [11].

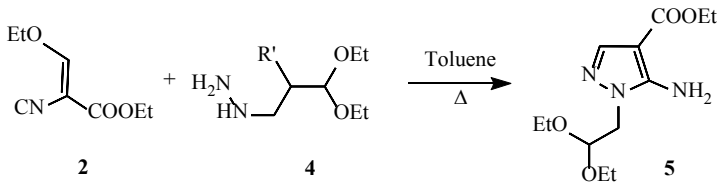
5-Amino-3-phenyl-1H-pyrazole **11** when reacted with hydroximoyl chloride **17** in ethyl alcohol at room temperature yields 3-nitroso-2-aryl-6-phenyl-1H-imidazolo [1,2-b]pyrazoles **18** (Scheme 9) [13].

Acylation of 5-amino-3-substituted-1H-pyrazole **19** using chloroacetyl chloride in basic medium produces 3H-imidazo[1,2-b]pyrazo-2-ol 20 (Scheme 10) [18].

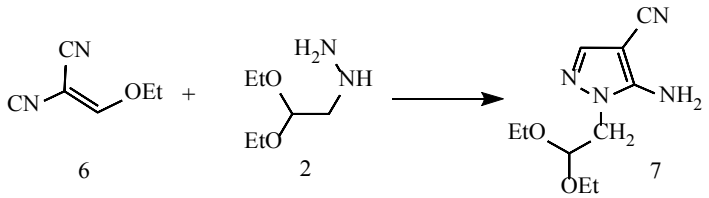
Heterocyclisation reaction of compound **11** by treatment with oxaldiimidoyl dichlorides **21** in THF-TEA yields 3H-imidazo[1,2-b]pyrazoles **22** (Scheme 11) [19].



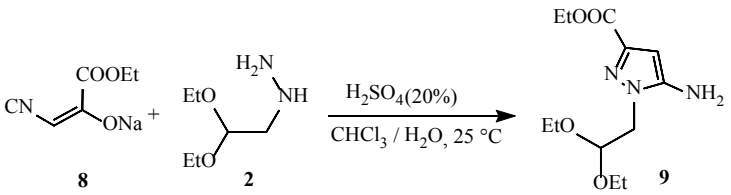
Scheme 1. Using 2-hydrazino-1-phenylethanol with (Ethoxymethylene) cyanoacetate, to produce 5-amino-N-aryl substituted pyrazoles [11].



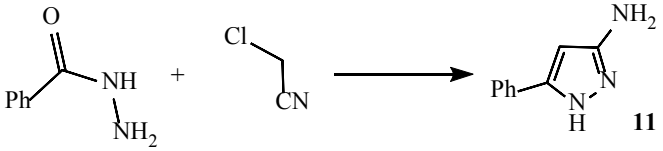
Scheme 2. Condensation of *α,β*-unsaturated cyanoacetate **2** with hydrazine derivative 4produced 5-amino-*N*-substituted-4-carboxylate pyrazole **5** [12].



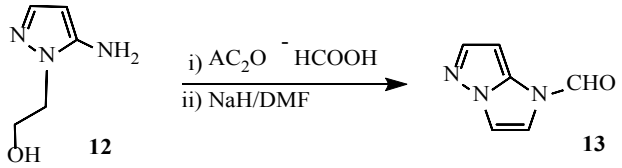
Scheme 3. Compound **2** treated with (ethoxy methylene)malononitrile to afford compound **7** [13].



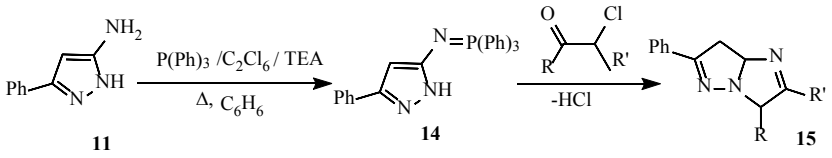
Scheme 4. Using compound **2** derivatives and ethyl cyano pyruvate **8** [14].



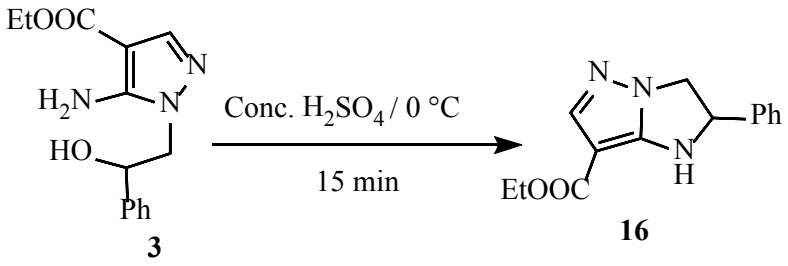
Scheme 5. Using chloroacetonitrile and benzoic acid hydrazide afforded5-amino pyrazole **11** [15].



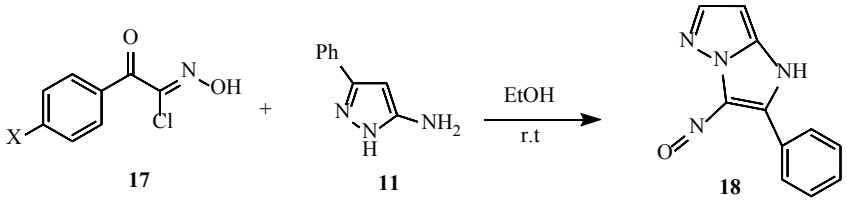
Scheme 6. Formylation of amino group of compound **12** [16].



Scheme 7. Carrying the aza-Wittig reaction of 5-amino-3-phenyl-1H-pyrazole **11** [17].

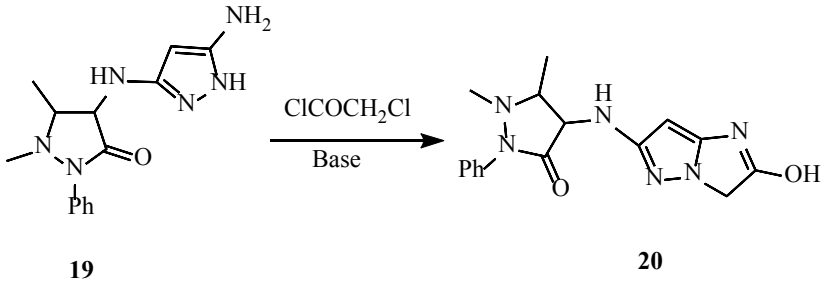


Scheme 8. Under dehydration of aminopyrazole **3** [11].

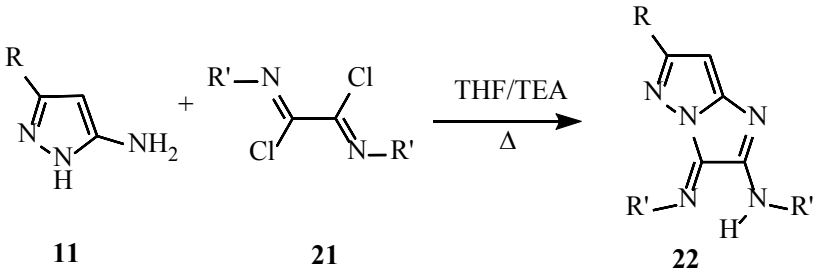


X= H, NO_2

Scheme 9. 1,3-Cycloaddition reaction with α-ketohydroximoyl chloride **17** [13].



Scheme 10. Acylation of 5-amino-3-substituted-1H-pyrazole **19** [18].



R = H, Me, Ph
R'= Ph, 4-MeC_6H_4 , $MeOC_6H_4$

Scheme 11. Heterocyclisation reaction of compound **11** [19].

Cycloaddition reactions of 3,5-diamino-1H-pyrazole-4-carbonitrile **23** with 3,4-dimethoxy benzonitrile **24** in the presence of 2,4-dihydro-2-oxo-1H-benzo [d][1,3]oxazine-7-carboaldehyde **25** results in the substituted imidazo[1,2-b] pyrazole-4-carbonitrile **26** (Scheme 12) [20].

Similarly, the cyclocondensation between aromatic aldehyde, 5-aminopyrazole **11** and isocyanide in acetonitrile with 4-toluene sulfonic acid as a catalyst at room temperature yields N-alkyl-2-aryl-5H-imidazolo[1,2-b]pyrazole-3-amine **27** (Scheme 13) [21].

Heterocyclisation of 5-amino-4-ethoxy-carbonyl amino-pyrazole **28** when fused at 200˚C for 24 h, yielded imidazole[4,5-c]pyrazole **30** gave the imidazole[4,5-c] pyrazole-5-thione **31** (Scheme 14) [22].

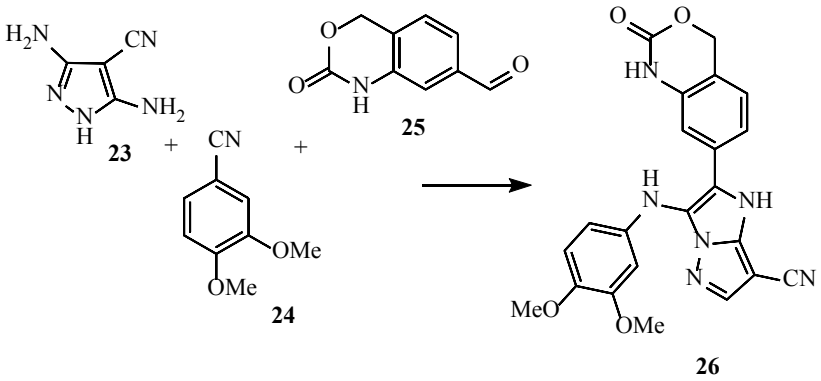
When compound **11** is treated with imidoyl chloride 32 in dry dioxane at room temperature in TEA, the substituted amine **33** is produced, which upon treatment with I2/KOH/DMF, yields 1-substituted-5-imino-4-iodo-pyrazole 34. Addition of CuI to **34** yields imidazo[1,2-c]pyrazole 35 (Scheme 15) [23].

Acylation of 5-amino-3-methyl-pyrazole **36** with acetic anhydride or benzoyl chloride yields 5-acyl amino pyrazoles **37**. Reduction of compound **37** with $LiAlH_4$ produces the corresponding 5-alkyl amino pyrazoles **38**. Nitrosation of **38** via amyl nitrile in HCl yields 5-alkylamino-4-nitrosopyrazole **39**, which upon cyclocondensation by reflux with dry pyridine yields imidazo[4,5-c]pyrazole **40** (Scheme 16) [24].

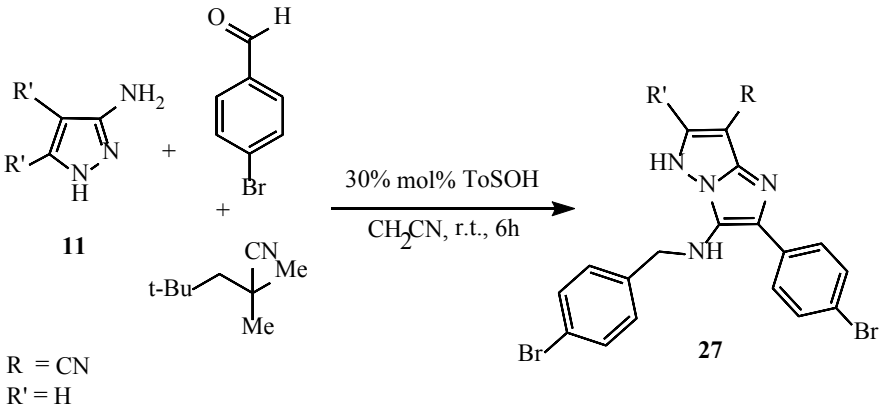
Interesting multi-component reactions (MCRs) were promoted via Knoevenagel condensation; 5-aminopyrazoles **41** have been utilized as 1,3-dinucleophilic starting material with either electron-withdrawing or electron-donating groups and various 1,3-dicarbonyl compounds in a one pot condensation in catalyzed water using ceric ammonium nitrate (CAN) produced a series of spiro[indoline-3,4'-pyrazolo[3,4-b]quinolone]dione derivatives **44** with good yields under mild conditions and eco-friendly general procedures as shown in Scheme 17 [25].

Around 24 examples of spiro-heterocyclic compounds were synthesised following this simple one-pot protocol, as illustrated in Scheme 18.

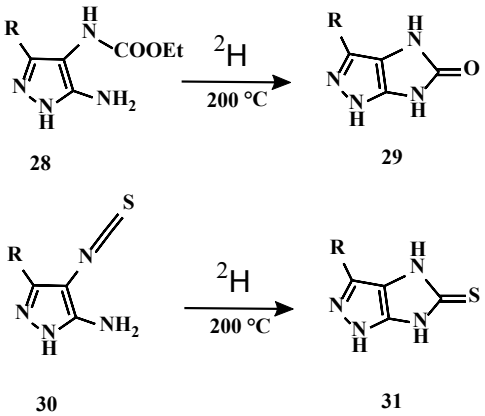
In a related synthesis of spiro-heterocyclic compounds which seems to be an improvement over the earlier procedure and is more region-selective, MCRs



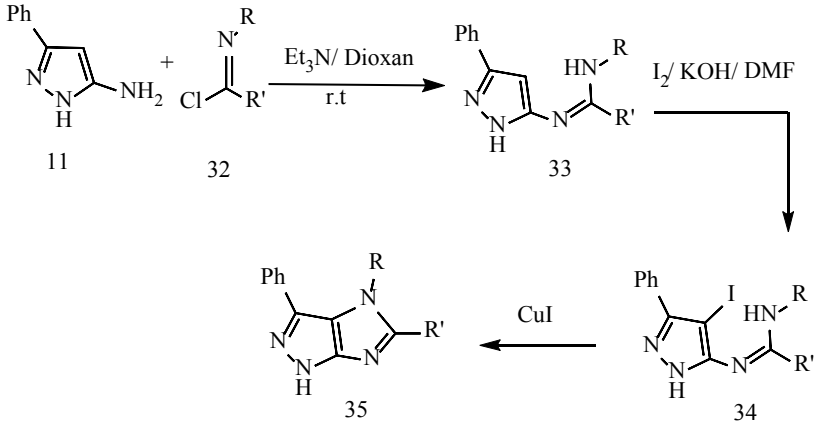
Scheme 12. Cycloaddition reactions of compound **23** [20].



Scheme 13. Cyclocondensation between compound **11** and an isocyanide [21].

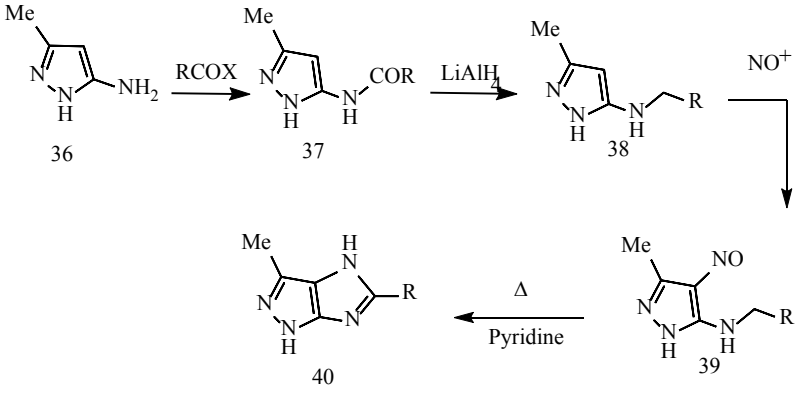


Scheme 14. Heterocyclisation of compounds **28** and **30** yielded imidazole[4,5-c]pyrazole derivatives [22].

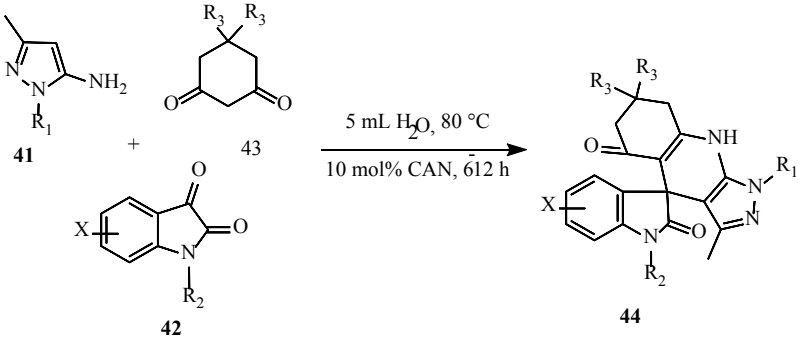


Scheme 15. Nucleophilic substitution of the halogen atom in the pyrazole nucleus **34** to synthesize Imidazo[4,5-c]pyrazoles **35** [23].

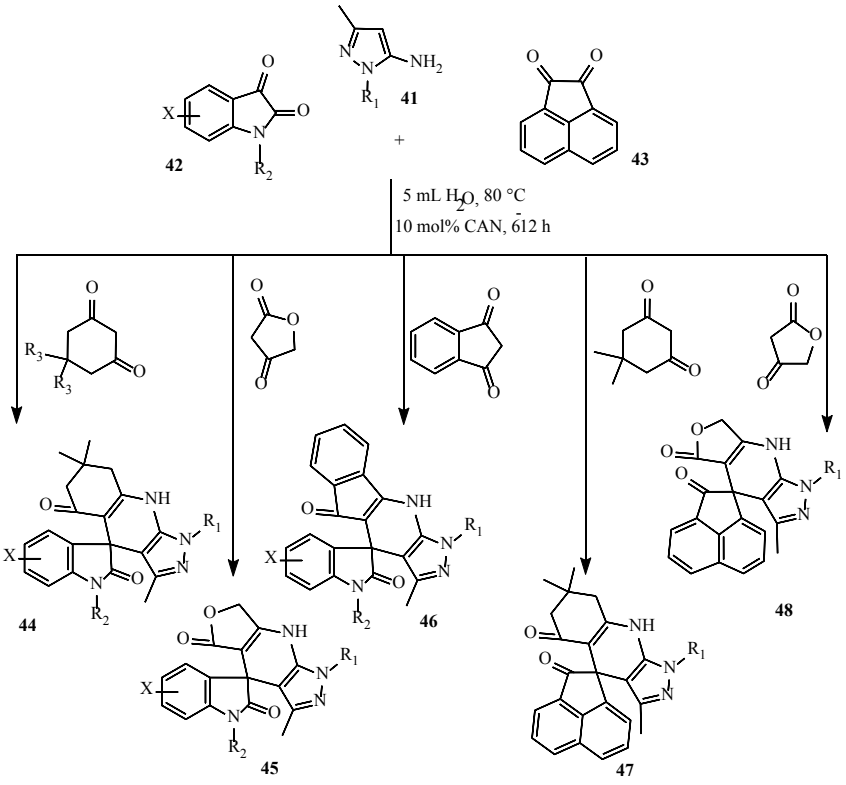
were accomplished using 5-amino-3-methyl-1-phenylpyrazole 49, *β*-diketones 50, and isatin **51** in a similar reaction catalyzed by water using p-TSA, which produced a series of derivatives of pyrazolopyridine-spiroindolinone (**Scheme 19**) [26].



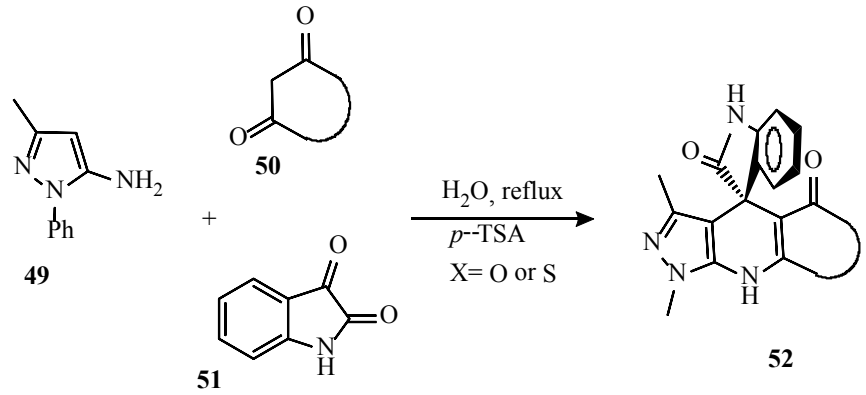
Scheme 16. Acylation of 5-amino-3-methyl-pyrazole **36** [24].



Scheme 17. Knoevenagel condensation of 5-aminopyrazoles **41** [25].



Scheme 18. Spiro-heterocyclic compounds were synthesized using compound **41** [25].



Scheme 19. A series of pyrazolopyridine-spiroindolinone derivatives were obtained using MCRs [26].

The structure-activity relationship (SAR) of amino-pyrazoles **54** as shown in Figure 1 has been approved as showing effective inhibition of p38a MAP kinase with very good cellular potency, which makes it an effective drug candidate for control of inflammatory disorders [27].

The use of 5-amino-pyrazole moiety led to the synthesis of designed scaffolds which produced potent selective p38α inhibiting drugs. The traditional procedure was used to prepare 5-amino-pyrazoles through condensation reaction of hydrazine **55** along with ethyl (ethoxymethylene) cyanoacetate **2** in ethyl alcohol in the presence of a base such as trimethylamine (Scheme 20). Hydrolysis to carboxylic acid before coupling with aniline using either HATU coupling or converting the acid carboxylic group to acid chloride and thereafter coupling it with aniline derivative **58** afforded good yields of the target compound **59** [27].

Successful one-pot synthesis of structural analogues to purines was achieved via a diazotization reaction which was carried out on 5-amino-1H-pyrazole-4-carbonitriles for the preparation of pyrazolo[3,4-d][1,2,3]triazin-4-ones 60 with moderately good to very good yields (Scheme 21). The reaction proceeded through diazoic acid or diazocarboxamide as intermediates. Various prepared pyrazolo[3,4-d][1,2,3]triazines have been shown to possess useful heterocyclic compounds with broad biological activities, for instance, anticonvulsant, antifungal, antiviral, and anticancer activities and antimicrobial effects [28] [29].

In addition, 5-amino-pyrazo derivatives were used in the synthesis of pyrazolo [3,4-d]pyrimidines in 244 examples [30]. Condensation of 5-heterylaminopyrazoles **64** with some carbonyl compounds in the presence of AcOH or Me3SiCl successfully produced pyrazolo[3,4-d]dihydropyrimidines 65 in good yields (Scheme 22). The best proposed mechanism explaining that reaction includes two steps: first, the reaction of 5-aminopyrazoles **62** with 2-halogenazines or azoles **63** in NaH/THF conditions, followed by ring closure with carbonyl compounds in Me3SiCl or AcOH medium.

4. Importance and Applications

Since the 1960s, the pyrazole moiety has been known to exhibit anticancer activity;

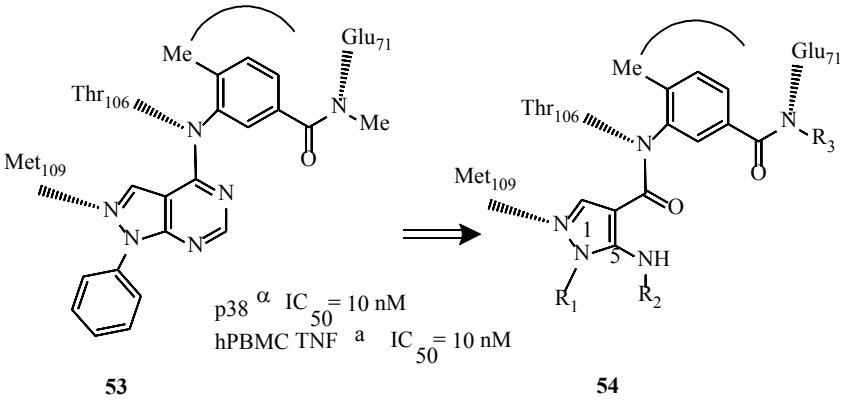
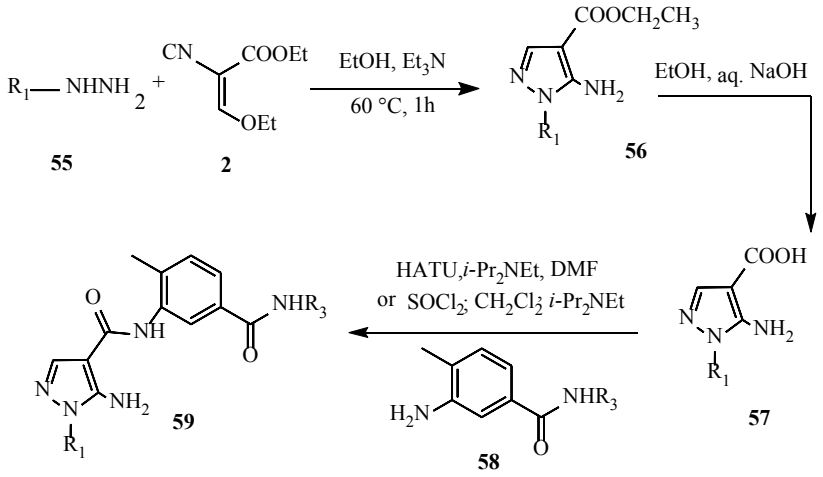
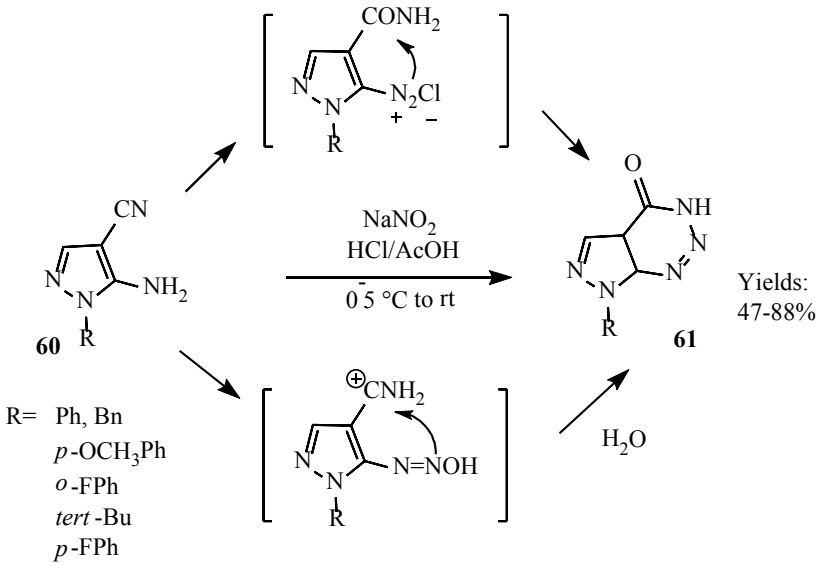


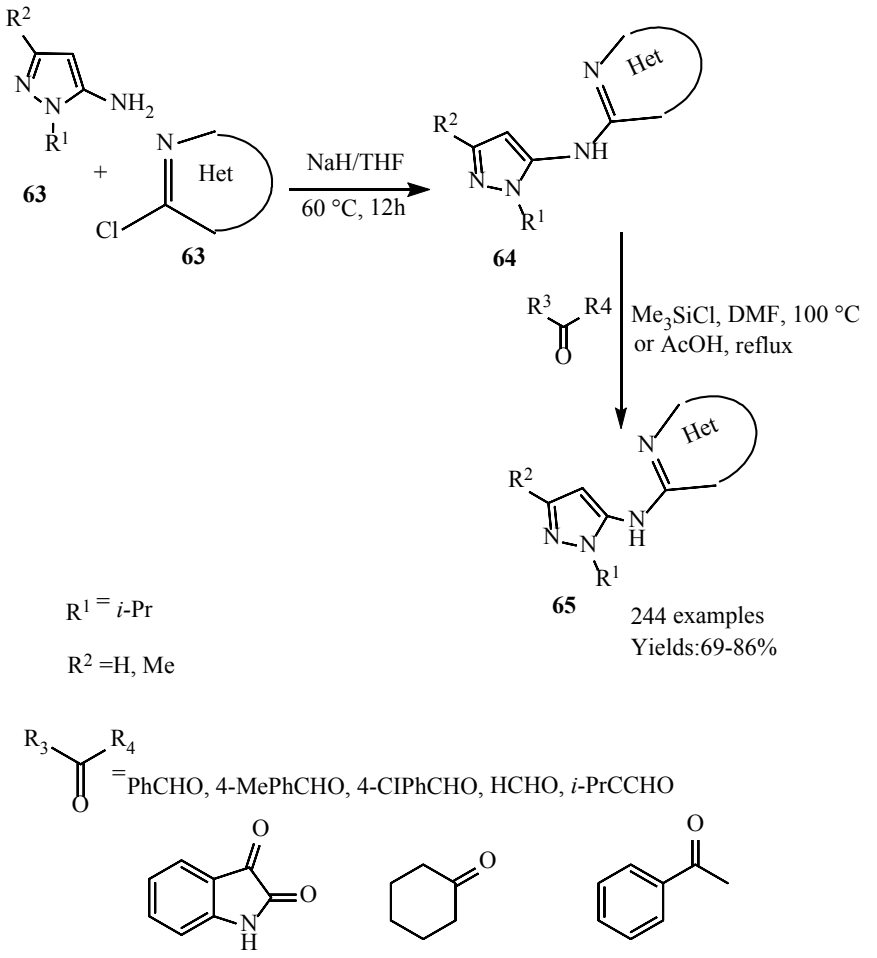
Figure 1. X-ray showed the expected pyrazolo-pyrimidine **53** and amino-pyrazoles **54**.



Scheme 20. HATU coupling of compound **57** with aniline derivative **58** afforded good yields of the amino-pyrazoles derivatives targeted **59** [27].



Scheme 21. One-pot diazotization reaction carried out on 5-amino-1H-pyrazole-4-carbonitriles **60** to synthesize pyrazolo[3,4-d][1,2,3]triazin-4-ones **61** [28].



Scheme 22. The arylation of 1-substituted-5-aminopyrazoles with electrophilic hetaryl-halides, then condensation of 5-hetarylaminopyrazoles with carbonyl compounds led to the synthesis of 244 examples [30].

it has also been shown to be an antitumor agent in Phase I studies. However, it was confirmed to be too toxic for human use, even in doses as low as 0.15 mmol/kg/day [31]. Researchers are keen to harness the powerful anticancer activity of pyrazoles without the toxic side effects, and synthesis of a variety of pyrazole derivatives are key to this pursuit [32]. Various derivatives have been tested, among them 1-thiocarbamoylpyrazole, 1-carboxamidopyrazole, which failed to show non-toxicity to humans, although it showed a remarkable anticancer clinical effect [33]. Compounds such as 5-amino-1-cyanoacetyl-3-(p-chlorophenyl)-pyrazole have been tested toward three human tumour cell lines: breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460), and CNS cancer (SF-268), and it has shown potent inhibition in growth of human tumour cell lines as well [34].

Pyrazole nucleosides and condensed pyrazole nucleosides possess various biological activities which make them powerful drug candidates, and these have been tested toward various diseases caused by DNA viruses [35].

Photographic material can be used to improve the absorption of imidazo[1,2-b]

pyrazoles [36] [37] [38] [39]. Also, some imidazo-pyrazoles have antiviral activity against herpes simplex virus type 1 infected mammalian cells [40] and show antimicrobial activity [41] [42]. 2,3-Dihydro-1H-imidazolo[1,2-b]pyrazoles exhibit in vivo effects on the proliferation of mouse leukemic cells [43] [44].

3-Amino-6-(B-D-ribofuranosyl)imidazo[4,5-c]pyrazole, used as a 5:5 fused analogue of adenosine was evaluated against two herpes viruses, herpes simplex virus 1 (HSV-1) and human cytomega covirus (HCMV) [45].

5. Conclusion

In summary, various routes exist for synthesis of 5-amino-*N*-substituted pyrazoles, which exhibit important chemical behavior towards electrophilic and nucleophilic reagents. Their tendency toward heterocyclisation reactions leads to the direct formation of imidazopyrazoles, which exhibit a variety of significant biological activities. The usefulness of 5-amino-*N*-substituted pyrazole molecules in the effort to obtain new heterocyclic compounds that have more accessible biocidal effects and enhancements is governed by substituent position and type.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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