Synthesis of various pyrazole-fused heterocyclic systems using pyrazole-4-carbaldehydes as versatile precursors

Ismail A. Abdelhamid*, Mahmoud A. E. Hawass, Sherif M. H. Sanad, and Ahmed H. M. Elwahy*

Chemistry Department, Faculty of Science, Cairo University, Giza-Egypt
E-mail: ismail_shafy@yahoo.com,aelwahy@hotmail.com

Abstract

The discovery of intriguing properties shown by a large number of pyrazole derivatives has sparked a surge in interest in pyrazole chemistry over the last decade. They exist in a variety of natural products, dyes, and as scaffolds in a variety of drugs and pharmaceutical active ingredients. This review demonstrated various methods for the construction of pyrazole-fused heterocycles using pyrazole-4-carbaldehydes as effective precursors. Heterocyclic compounds mentioned in this review are arranged into categories based on the size of the heterocyclic ring as well as the position and number of the heteroatoms.

Keywords: Pyrazole-4-carbaldehydes, synthesis, cyclization, cyclocondensation, pyrazole-substituted heterocycles
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1. Introduction

Heterocycles are an essential class of compounds that make up more than half of all known organic compounds. They can be found in a variety of natural products and biomolecules such as hormones, antibiotics, alkaloids, vitamins, and so on. Heterocyclic compounds are of great concern in our everyday life. They are used in a variety of industries, including agrochemicals, pharmaceuticals, and veterinary products. They are also used as starting materials for the production of sanitizers, developers, anti-ordinates, corrosion inhibitors, and other products.\(^1\)\(^-\)\(^1\)\(^2\)\(^-\)\(^1\)\(^3\) Nitrogen-containing heterocycles constitute the core structures of a variety of biologically active compounds and have a wide range of applications in chemistry, biology, and other fields. Many naturally occurring N-heterocyclic compounds have physiological and pharmacological properties and are components of a wide range of biologically important molecules, including vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes, and agrochemicals.\(^4\)\(^,\)\(^1\(^3\)\(^-\)\(^1\)\(^8\) Furthermore, heterocycles containing nitrogen are essential in coordination chemistry.\(^1\(^9\) Pyrazoles are aromatic heterocycles with two nitrogen atoms in their five-membered rings that are well-known. They are a significant heterocyclic family that includes a wide variety of chemical, biological, agrochemical, and pharmaceutical properties.\(^8\)\(^,\)\(^2\(^0\)\(^-\)\(^2\(^4\) Several drugs have been produced from pyrazole derivatives.\(^2\(^5\)\(^-\)\(^3\(^0\) The use of pyrazole derivatives in semiconductors, liquid crystals, and organic light-emitting diodes applications have been extensively investigated.\(^3\(^1\)\(^-\)\(^3\(^5\) In continuation of our interest in reviewing various synthetic approaches to a variety of heterocycles\(^3\(^6\)\(^-\)\(^5\(^1\), this review highlights the utility of pyrazole-4-carbaldehydes in the preparation of pyrazole-fused heterocyclic systems over the last two decades. Very recently, we reviewed the usefulness of pyrazole-4-carbaldehydes as versatile precursors for different pyrazole-substituted heterocyclic systems.\(^5\(^2\) Heterocyclic compounds mentioned in this review are arranged based on the size of the heterocyclic ring as well as the position and number of the heteroatoms.

2. Synthesis of Fused Pyrazoles

2.1. Pyrazole fused within a bicyclic system
2.1.1. Fused [5-5] system with three heteroatoms. 2.1.1.1. Pyrrolo[2,3-c]pyrazole. Aly et al.\(^5\(^3\) reported that heating of 3-aryl-1-phenyl-1H-pyrazol-4-carbaldehydes 1 with ethyl azidoacetate 2 in ethanol followed by
heating in toluene at reflux gave pyrrolo[2,3-c]pyrazole derivatives 3a and 3b in 30 and 35% yield, respectively (Scheme 1).


2.1.1.2. Thieno[2,3-c]pyrazole. Methyl 1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 5 was prepared by the reaction of 5-chloro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde 4 with methyl thioglycolate 2 in ethanol in the presence of anhydrous sodium carbonate\textsuperscript{54} (Scheme 2).

Scheme 2. Synthesis of methyl-1,3-diphenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 5.

2.1.2. Fused [5-5] system with four heteroatoms. 2.1.2.1. Pyrazolo[3,4-c]pyrazole. Aly et al.\textsuperscript{55} reported that treatment of 5-azido-1-phenyl-3-pyridin-4-yl-1H-pyrazole-4-carbaldehyde 6 with hydrazine hydrate 7 in the presence of acetic acid in ethanol at reflux yielded 1-phenyl-3-pyridin-4-yl-1,6-dihydropyrazolo[3,4-c]pyrazole 8. On the other hand, treatment of 7 with hydrazine hydrate 7 at room temperature in the presence of iodine afforded 6-phenyl-4-pyridin-4-yl-6H-pyrazolo[3,4-c]pyrazol-2-ylamine 9 (Scheme 3).

2.1.3. Fused [5-6] system with three heteroatoms. 2.1.3.1. Pyrazolo[3,4-b]pyridine. Zheng et al.\textsuperscript{56} reported that one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes 6a and 6b with the appropriate arylethanone 2a–c, acetone 2d, acetylacetone 2e or benzoylaceton 2f in a solution of ethanolic KOH afforded the corresponding pyrazolo[3,4-b]pyridine derivatives 10a-j (Scheme 4).

![Scheme 4. Synthesis of pyrazolo[3,4-b]pyridine derivatives 10a-j.](image)

Condensation of 5-amino-1H-pyrazole-4-carbaldehyde 11 with propiophenone 2j afforded 3-(4-aryl)-5-methyl-6-phenyl-1H-pyrazolo[3,4-b]pyridine derivatives 12\textsuperscript{57}. On the other hand, condensation of 5-aminopyrazole-4-carbaldehydes 11 and unsymmetric dialkylketones 2f yielded a mixture of isomeric pyrazolo[3,4-b]pyridine derivatives 13 and 14\textsuperscript{58}. A series of 1,3,6-trisubstituted and 1,3,5,6-tetrasubstituted pyrazolo[3,4-b]pyridines 15 has been synthesized by condensation of 11 with α-methylene ketones such as acetone 2d or acetophenones 2a with potassium hydroxide as a basic catalyst\textsuperscript{58} (Scheme 5).

![Scheme 5. Synthesis of pyrazolo[3,4-b]pyridine derivatives 12, 13, 14 and 15.](image)

Friedländer condensation of 5-amino-1H-pyrazole-4-carbaldehyde 11 with acetonitrile derivatives 2 in ethanol in the presence of a catalytic amount of piperidine yielded the corresponding pyrazolo[3,4-b]pyridine-5-carbonitriles 16\textsuperscript{58,59}. 6-Aminopyrazolo[3,4-b]pyridines 18 were obtained by the condensation of 1 with the corresponding cyanomethyl derivatives 17\textsuperscript{57,59–61} (Scheme 6).

Panda et al.\(^6\) reported that treatment of 5-amino-1H-pyrazole-4-carbaldehyde 11a and 11b with various active methylene compounds 17a-c in the presence of an excess of sodium methoxide heated at reflux in methanol gave the corresponding pyrazolo[3,4-b]pyridines 7a-f (Scheme 7).

\[
\begin{align*}
\text{NaOCH}_3, \text{CH}_3\text{OH} & \quad \text{reflux} \\
\text{R}^1\text{CH}_2\text{CN} & \rightarrow \\
\text{R} = \text{C}_6\text{H}_5, \text{CH}_3; \text{R}^1 = \text{CONH}_2, \text{CN}, \text{CO}_2\text{Et}; \text{R}^2 = \text{CONH}_2, \text{CN}; \text{R}^3 = \text{NH}_2, \text{OH}.
\end{align*}
\]

Scheme 7. Synthesis of pyrazolo[3,4-b]pyridines 19a-f.

5-Amino-1H-pyrazole-4-carbaldehyde 11 reacted with diethyl malonate 19 to give the corresponding ethyl 6-oxo-6,7-dihydropyrazolo[3,4-b]pyridine-5-carboxylate derivatives 20.\(^58,60\) On the other hand, condensation of 11 with dimethyl-3-oxopentanedioate 21 yielded a mixture of methyl 6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylates 22 and methyl 6-(2-methoxy-2-oxoethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylates 23.\(^57\) Condensation of 11 with 5-ketoesters 24 in the presence of piperidine as a basic catalyst yielded pyrazolo[3,4-b]pyridine-5-carboxylates 25.\(^58\) (Scheme 8).

Babaqi et al.\(^63\) reported that 1-aryl-3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-ones 26a and 26b were prepared by Knoevenagel condensation of 5-chloro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde 4 with acetoephone or p-methylacetoephone 2d. Treatment of 26a and 26b with cyclohexanone 27 or 1,3-diphenyl-2-pyrazolin-5-one 29 afforded 2-(1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)cyclohexan-1-one 28 or 4-(1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one 30, respectively, via Michael addition followed by cyclization and subsequent diarylation (Scheme 9).


The base-catalyzed Michael addition of 26a and 26b with ethyl acetoacetate 24 followed by cyclization under the same conditions yielded ethyl 4-(2-aryl-2-oxoethyl)-6-methyl-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate derivatives 31a and 31b. On the hand reaction of diethyl malonate 19 with 26a and b under the same conditions gave ethyl 4-(2-aryl-2-oxoethyl)-6-oxo-1,3-diphenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylates 32a and b (Scheme 10).
El-Metwally and Khalil\textsuperscript{64} reported that azidoformylpyrazole 6 was fused with ethyl acetoacetate 24 at 150°C to give 5-acetyl-1,3-diphenyl-1,7-dihydro-6\textit{H}-pyrazolo[3,4-\textit{b}]pyridin-6-one 33 which exists as a mixture of keto-enol forms (Scheme 11).

2.1.4. Fused [5-6] system with four heteroatoms. 2.1.4.1. Pyrazolo[3,4-d]pyrimidine. Molina \textit{et al.}\textsuperscript{66} reported that treatment of 5-azido-3-methyl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehyde 6 with aromatic amines 35 in ethanol gave the corresponding 1-(5-azido-3-methyl-1-phenyl-1\textit{H}-pyrazol-4-yl)-\textit{N}-arylmethanimines 36\textsubscript{a} and \textsubscript{b}. The preparation of the desired iminophosphoranes 38 and 40 was accomplished through the classical Staudinger reaction of 5-azidopyrazoles 6 and 36 with triphenylphosphine 37, respectively. The reaction of
iminophosphorane 40 with isocyanates 41 resulted in the formation of the corresponding pyrazolo[3,4-d]pyrimidines 39. The 40 → 19 conversion involves an initial aza-Wittig reaction between 5-((triphenylphosphaneyldene)amino)-1H-pyrazole-4-carbaldehyde 40 and isocyanate 41 to give a carbodiimide which undergoes electrocyclic ring closure to give an unstable 3-methyl-N,1-diphenylpyrazolo[3,4-d][1,3]oxazin-6-imine 42. The latter compound by a typical Dimroth rearrangement undergoes ring-opening and closure to furnish 39 in a 15% yield. However, compounds 39 were also prepared in good yields from N-(3-methyl-1-phenyl-4-((phenylimino)methyl)-1H-pyrazol-5-yl)-1,1,1-triphenylphosphanimine 38 and carbon dioxide (Scheme 13).

Triphenylphosphanimine 44 was prepared by the reaction of 40 and (p-nitrophenyl)hydrazine 43. The reaction of triphenylphosphanimine 44 with isocyanates 41 gave the pyrazolo[3,4-d]pyrimidines 45 (Scheme 14).


When triphenylphosphanimine 38 were treated with carbon disulfide 46, pyrazolopyrimidines 48 were formed. The mechanisms of the conversion of 38 into 48 are supported by the isolation in some cases of the isothiocyanate 47 which by heating in dry toluene at reflux temperature was converted into the corresponding
fused pyrimidine 48. The reaction of triphenylphosphanimines 38 with isocyanates 41 gave the corresponding pyrazolo[3,4-\textit{d}]pyrimidines 49.

On the other hand, the reaction of triphenylphosphanimines 38 with acyl chlorides 50 gave the corresponding pyrazolo[3,4-\textit{d}]pyrimidinium salts 51 (Scheme 15).\(^6^6\)

The intermolecular heterocyclization from \(N'-(4\text{-formylypyrazol}-5\text{-yl})\text{formimidamide} 52\) with various amines\(^6^7\) or cyanamide (NH\(_2\)CN) in acidic solution at reflux\(^6^8\) afforded the corresponding 1-aryl-3-phenyl-1\(\text{H}\)-pyrazolo[3,4-\textit{d}]pyrimidine 53 (Scheme 16).

\begin{align*}
\text{Scheme 15. Synthesis of pyrazolo[3,4-\textit{d}]pyrimidines 48, 49 and 51.}
\end{align*}

\begin{align*}
\text{Scheme 16. Synthesis of 1\(\text{H}\)-pyrazolo[3,4-\textit{d}]pyrimidines 53.}
\end{align*}

Cyclization of 5-aminopyrazole-4-carbaldehyde 11 with formamide\(^6^9,7^0\) or benzamide\(^7^0\) and phosphorus tribromide (PBr\(_3\))\(^6^9\) afforded pyrazolo[3,4-\textit{d}]pyrimidines 54. A series of 11 reacted with reactive species 55 generated from the reaction of HCHO and PBr\(_3\). The reaction proceeds by an amidination reaction to give the intermediate 56 followed by heterocyclization to give 54\(^6^9\) (Scheme 17).
Scheme 17. Synthesis of pyrazolo[3,4-d]pyrimidines 54.

2.1.4.2. Pyrazolo[3,4-d]pyridazine. Matiichuk et al.\textsuperscript{71} reported that reactions of ethyl 1-aryl-4-formyl-1H-pyrazole-3-carboxylates 1 with hydrazine 7 and methylhydrazine 43 led to the formation of the corresponding pyrazolo[3,4-d]pyridazin-4-ones 57 and 58, respectively (Scheme 18).

Scheme 18. Synthesis of pyrazolo[3,4-d]pyridazin-4-ones 57 and 58.

2.1.5. Fused [5-6] system with five heteroatoms. 2.1.5.1. Pyrazolo[3,4-d][1,2,3]triazine. El-Metwally and Khalil\textsuperscript{64} reported that pyrazole-4-carbaldehyde 4 was treated with sodium azide 59 in DMSO to give 5-azido-1,3-diphenyl-1H-pyrazole-4-carbaldehyde 6\textsuperscript{72} which reacted with hydrazine hydrate 7 to give pyrazolo[3,4-d][1,2,3]triazine 60\textsuperscript{64} (Scheme 19).

Scheme 19. Synthesis of pyrazolo[3,4-d][1,2,3]triazines 60.
2.2. Pyrazole fused within a tricyclic system

2.2.1. Fused [5-5-6] system with three heteroatoms. 2.2.1.1. Clopenta[b]pyrazolo[4,3-e]pyridine. Jachak et al.\textsuperscript{70} reported that the cyclocondensation of 5-amino-1H-pyrazole-4-carbaldehyde 11 with cyclopentanone 61 yielded cyclopenta[b]pyrazolo[4,3-e]pyridines 62 in ethanolic KOH at reflux (Scheme 20).

\[
\begin{array}{c}
\text{11a,b} \xrightarrow{\text{KOH/ EtOH 1 h, reflux}} \text{62a,b} \\
\text{Ar} = 4-\text{Cl-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4.
\end{array}
\]


Barreiro et al.\textsuperscript{61} reported that stirring of 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 11 in ethanol with hydroxylamine hydrochloride 63 and pyridine followed by reaction with POCl\textsubscript{3} at reflux gave 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile 64. 3-Methyl-1-phenyl-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[4,3-e]pyridin-4-amine 65 was then obtained from Friedländer condensation of 64 with cyclopentanone 61(Scheme 21).

\[
\begin{array}{c}
\text{11} \xrightarrow{\text{1) NH}_2\text{OH.HCl / pyridine}} \text{63} \xrightarrow{\text{EtOH, rt 2 h}} \text{64} \xrightarrow{\text{2) POCl}_3/ \text{reflux}} \text{61} \\
\text{64} \xrightarrow{\text{AlCl}_3 \text{ClCH}_2\text{CH}_2\text{Cl reflux, 3 h.}} \text{65}
\end{array}
\]


Zheng et al.\textsuperscript{56} reported that a one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes 6 with cyclopentanone 61 in a solution of ethanolic KOH afforded the corresponding 1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[4,3-e]pyridines 66 (Scheme 22).

\[
\begin{array}{c}
\text{6} \xrightarrow{\text{KOH-EtOH Reflux}} \text{61} \xrightarrow{\text{R}^1} \text{66}
\end{array}
\]

\[
\text{R}^1 = \text{CH}_3, \text{C}_6\text{H}_5.
\]

2.2.1.2. Pyrazolo[3,4-e]indolizine. The reaction of 5-(pyrrolidin-1-yl)-1H-pyrazole-4-carbaldehyde 67 with methylene active nitriles 17 afforded 2-((5-(pyrrolidin-1-yl)pyrazol-4-yl)methylene derivatives 68. The latter compound was then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding pyrazolo[3,4-e]indolizine 69\textsuperscript{73,74} (Scheme 23).

![Scheme 23. Synthesis of pyrazolo[3,4-e]indolizines 69.](image)

\[ R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7; R^1 = \text{CN, CONH}_2, \text{CSNH}_2; R^2 = \text{CONH}_2, \text{CSNH}_2. \]

2.2.2. Fused [5-5-6] system with five heteroatoms. 2.2.2.1. Dipyrazolo[3,4-b:4',3'-e]pyridine. 2.2.2.2. Isoazolo[5,4-b]pyrazolo[4,3-e]pyridine. 2.2.2.3. Isothiazolo[5,4-b]pyrazolo[4,3-e]pyridine. Abramov et al.\textsuperscript{75} reported that [1+1] condensation reaction of 5-amino-1,2-azoles 70a-d with 5-chloropyrazole-4-carbaldehydes 4a-c at reflux in toluene afforded the corresponding dipyrazolo[3,4-b:4',3'-e]pyridines, isoazolo[5,4-b]pyrazolo[4,3-e]pyridine and isothiazolo[5,4-b]pyrazolo[4,3-e]pyridine 71a-f (Scheme 24).


\[ R^1 = \text{CH}_3, \text{C}_6\text{H}_5; R^2 = \text{C}_6\text{H}_5, \text{CH}_3; R^3 = \text{CH}_3, \text{C}_6\text{H}_5; X = \text{NC}_6\text{H}_5, \text{O, S, NCH}_3. \]

2.2.3. Fused [5-6-6] system with three heteroatoms. 2.2.3.1. Pyrazolo[3,4-b]quinoline. Zheng et al.\textsuperscript{56} reported that one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes 6 with cyclohexanone 27 or dimedone 72 in a solution of ethanolic KOH afforded the corresponding 5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolines 73 and 3,7,7-trimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-b]quinolin-5-one 74, respectively (Scheme 25).
Scheme 25. Synthesis of tetrahydro-1H-pyrazolo[3,4-b]quinolines 73 and 74.

Condensation of cyclohexanone 27a\textsuperscript{62,70} or 2-methyl-1-cyclohexanone 27b\textsuperscript{70} with 5-amino-1H-pyrazole-4-carbaldehyde 11 afforded pyrazolo[3,4-b]quinoline derivatives 75\textsuperscript{62,70}. Heating 11 with dimedone 72 furnished pyrazolo[3,4-b]quinolinone derivatives 76\textsuperscript{70} (Scheme 26).

Scheme 26. Synthesis of pyrazolo[3,4-b]quinolinone derivatives 75 and 76.

Reaction of 5-chloropyrazole-4-carbaldehydes 4 and 4-substituted aniline 35a-1 under various conditions afforded the corresponding 1,3,6-trimethyl-1H-pyrazolo[3,4-b]quinoline 77\textsuperscript{76-81}. On the other hand, fusion of 4-ethoxyaniline 35j with 1-phenyl-3-methyl-5-chloro-pyrazole-aldehyde 4 afforded 8-ethoxy-3-methyl-1-phenyl-1H-pyrazolo[4,3-c]quinoline 78 or 6-ethoxy-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline 79\textsuperscript{82} (Scheme 27).
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**Scheme 27.** Synthesis of pyrazolo[3,4-b]quinolines 77 and 78 and 1H-pyrazolo[3,4-c]quinoline 79.

Gondek et al.\(^8^3\) reported that aniline derivative 79 and 5-chloropyrazole-4-carbaldehydes 4 were heated together at 140–190°C for 60 min to get pyrazolo[3,4-b]quinolines 80 (Scheme 28).

**Scheme 28.** Synthesis of pyrazolo[3,4-b]quinolines 80.

Barreiro et al.\(^6^1\) reported that stirring of 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 11 in ethanol at room temperature with hydroxylamine hydrochloride and pyridine to afforded the oxime intermediate. Next, 5-amino-3-methyl-1-phenyl-1H-5-pyrazole carbaldehyde oxime was reacted with phosphorus oxychloride at reflux to give 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile 81. 3-Methyl-1-phenyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolin-4-amine 82 was obtained from Friedländer condensation of 81 with cyclohexanone 27 (Scheme 29).
2.2.3.2. Pyrazolo[4,3-c]quinoline. Christodoulou et al. reported that oxidation of the pyrazole-carbaldehydes 1 with NaOCl in the presence of sulfamic acid as a scavenger, furnished the corresponding acids 83 which were treated with methoxylamine hydrochloride 63 in the presence of the uronium-coupling reagent O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) to provide amides 84. The latter compounds were cyclized by phenyliodine bis(trifluoroacetate) PIFA and trifluoroacetic acid (TFA), to furnish the target 5-methoxy-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-ones 85 (Scheme 30).


Bratenko et al. reported that reduction of 3-(2-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 using NaBH₄ afforded (3-(2-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methanol 87. Compound 87 reacted with thionyl chloride 88 to afford 4-(chloromethyl)-3-(2-chlorophenyl)-1-phenyl-1H-pyrazole 89 which was converted into N-[3-(2-chlorophenyl)-pyrazol-4-yl]methylamine 90 upon treatment with sodium azide 59 and subsequent reduction with Raney Ni. The condensation of aldehyde 1 with alkylamines 35 provided azo-methines 92 which on reduction using NaBH₄ gave N-alkyl-N-pyrazolylmethylamines 93. Heating of N-pyrazolylmethylamine 90 and N-alkyl-N-pyrazolylmethylamines 93 in boiling DMF in the presence of potassium carbonate led to the formation of the target 2-phenyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolines 91 (Scheme 31).
Baraldi et al.\cite{87} reported that the oxidation of the pyrazole-4-carbaldehydes 1 with KMnO$_4$ yielded the pyrazole-4-carboxylic acids 83 that were transformed to the respective esters 94 in a mixture of ethanol and sulfuric acid. Hydrogenation of 1a using hydrogen/Pd-C in ethanol afforded 2-phenyl-2H-pyrazolo[4,3-c]quinolines 96. Reduction of 94 with hydrogen/Pd-C or using iron powder and concentrated solution of HCl afforded 2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-ones 95 (Scheme 32).

**Scheme 32.** Synthesis of 4H-pyrazolo[4,3-c]quinolin-4-ones 95.

2.2.3.3. Pyrazolo[4,3-c]quinolizine. The reaction of 5-(piperidin-1-yl)-1H-pyrazole-4-carbaldehyde 97 with active methylene nitriles 17 afforded arylidene 98 which then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding 1,4,5,5a,6,7,8,9-octahydropyrazolo[4,3-c]quinolizines 99\cite{73,74} (Scheme 33).

2.2.4. Fused [5-6-6] system with four heteroatoms. 4.2.4.1. Pyrazolo[3,4-b][1,6]naphthyridine. Jachak et al.\textsuperscript{70} reported that the cyclocondensation of 5-amino-1H-pyrazole-4-carbaldehyde 11 with N-benzyl-4-piperidone 100 yielded pyrazolo[3,4-b][1,6]naphthyridines 101 in good yield (Scheme 34).

Scheme 34. Synthesis of pyrazolo[3,4-b][1,6]naphthyridines 101.

2.2.4.2. Pyrazolo[4',3':5,6]pyrido[2,1-c][1,4]oxazine. Reaction of 5-morpholino-1H-pyrazole-4-carbaldehydes 102 with active methylene nitriles afforded arylidene derivatives 103 which then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding 5-cyano-pyrazolo[4',3':5,6]pyrido[2,1-c][1,4]oxazine-5-carboxamides 104\textsuperscript{73,74} (Scheme 35).


2.2.5. Fused [6-5-5] system with two heteroatoms. 2.2.5.1. Indeno[1,2-c]pyrazole. El-Aal et al.\textsuperscript{88} reported that 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxylic acid 105 were obtained utilizing KMnO\textsubscript{4} oxidation of the
5-chloro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde 4. Heating 105 in absolute ethanol at reflux and concentrated sulfuric acid afforded ethyl-5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxylate 106 which were smoothly reacted with the Grignard reagent to give alkanols 107. Cyclization of the 2-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)propan-2-ol 107 by a Friedel–Crafts-type ring closure afforded the 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-c]pyrazole 108 (Scheme 36).

**Scheme 36.** Synthesis of 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-c]pyrazole 108.

2.2.6. Fused [6-5-8] system with three heteroatoms. 2.2.6.1. Benzo[b]pyrazolo[3,4-d]azocine. Baraldi et al.\(^8\) reported that reaction of 3-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 with triphenyl-\(\lambda^5\)-phosphanylidene-acetic acid ethyl ester (Wittig reaction) afforded ethyl-3-(3-(2-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylate 109 which was hydrogenated to give ethyl-3-(3-(2-aminophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylate 110. Subsequent treatment of 110 with NaH afforded 2-phenyl-2,4,5,7-tetrahydro-6H-benzo[b]pyrazolo[3,4-d]azocin-6-one 111 (Scheme 37).

**Scheme 37.** Synthesis of 6\(H\)-benzo[b]pyrazolo[3,4-d]azocin-6-one 111.

2.2.7. Fused [6-6-5] system with two heteroatoms. 2.2.7.1. Naphtho[2,3-d]imidazole. Reddy et al.\(^9\) reported that naphtho[2,3-d]imidazoles 113 were synthesized by the reaction of pyrazole-4-carbaldehyde 1 with naphthalene-2,3-diamine 112 in ethanol and sodium meta-bisulphite (Na\(_2\)S\(_2\)O\(_5\)) (Scheme 38).

2.2.8. Fused [6-6-5] system with three heteroatoms

2.2.8.1. Chromeno[2,3-c]pyrazole. Heterocyclic ionic liquid (IL) promoted C-H bond oxidative cross-coupling reaction for the intramolecular annihilation of 5-(aryloxy)-1H-pyrazole-4-carbaldehydes 114 to chromeno[2,3-c]pyrazol-4(1H)-ones 115 (Scheme 39).

![Scheme 39](image_url)


2.2.8.2. Chromeno[4,3-c]pyrazole. Under a Cu(0)/Selectfluor catalyzed system, a range of 3-methyl-1,5-diphenyl-1H-pyrazole-4-carbaldehydes 116 could be intramolecularly lactonized to chromeno[4,3-c]pyrazoles 117 in moderate to good yields (55-72%, 117a-e, Scheme 40, Table 1). For substrate 116 possessing two phenyl rings adjacent to the formyl group, the cross-dehydrogenative C-O coupling reaction predominantly took place in the phenyl ring substituted with stronger electron-withdrawing groups (117g-117j, Scheme 40, Table 1). When 116f was used as the substrate, the reaction gave a regioisomeric mixture of 117f and 117f' in a total yield of 62% with a molar ratio of 1:0.41 determined by NMR analyses (116f, Scheme 40, Table 1). Similarly, the intramolecular lactonization of 116k resulted in a regioisomeric mixture of 117k and 117k' in a total yield of 63% with a molar ratio of 1:0.94 (116k, Scheme 40, Table 1).
Scheme 40. Synthesis of chromeno[4,3-\(c\)]pyrazoles 117.

Table 1. Cu(0)/Selectfluor system-catalyzed double C-H activation/oxygen insertion of 5-arylpyrazole-4-carbaldehydes 116a,b

| 117a (67%) | 117b (70%) | 117c (72%) | 117d (55%) | 117e (60%) |
| 117f | 117f* | 117g (66%) | 117h (63%) |
| 117i (50%) | 117j (45%) | 117k | 117k* |

Lokhande et al.\textsuperscript{92} reported the synthesis of 3-(2-(allyloxy aryl)-1-phenyl-1\(H\)-pyrazole-4-carbaldehydes 118a-g \textit{via} stirring of pyrazole-4-carbaldehydes 1a-g with allyl bromide in DMSO, K\(_2\)CO\(_3\). When 3-(2-hydroxyaryl)pyrazole-4-carbaldehydes 1a-g or 3-(2-(allyloxyaryl)pyrazole-4-carbaldehydes 118a-g were heated at 120 °C in DMSO in the presence of iodine (10 mol %) and 4-5 drops of concentrated H\(_2\)SO\(_4\), 2-arylpyrazolo[4,3-c]coumarin derivatives 119a-g were obtained in good yields. On the other hand, when
3-(2-hydroxyaryl)pyrazole-4-carbaldehydes 1a-c or 3-(2-(allyloxyaryl)pyrazole-4-carbaldehydes 118a-c were heated at 120 °C DMSO in the presence iodine (1.2 equiv.) and 4-5 drops of concentrated H₂SO₄ gave 2-phenylchromeno[4,3-c]pyrazol-4(2H)-one derivatives 120a-c (Scheme 41).

**Scheme 41.** Synthesis of 2-phenylchromeno[4,3-c]pyrazol-4(2H)-one derivatives 119 and 120.

3-(2-Hydroxy-substitutedphenyl)-1-aryl-1H-pyrazole-4-carbaldehydes 1 were cyclized to 4-ethoxy-2,4-dihydrochromeno[4,3-c]pyrazoles 121 upon treatment with ethanol containing a catalytic amount of hydrochloric acid³³ or sulfuric acid³⁴ to 4-ethoxy-2,4-dihydrochromeno[4,3-c]pyrazoles 121³³,³⁴ (Scheme 42).

**Scheme 42.** Synthesis of 4-ethoxy-2,4-dihydrochromeno[4,3-c]pyrazoles 121.
2.2.8.3. Thiochromeno[2,3-c]pyrazole. Li et al.\textsuperscript{90} reported that intramolecular cross-coupling reaction of 3-methyl-1-phenyl-5-(p-tolylthio)-1H-pyrazole-4-carbaldehyde 122 using 1,3-dibutyl-1H-benzo[d][1,2,3]triazol-3-ium bromide IL and tert-butyl hydroperoxide (TBHP) as an oxidant afforded 3,6-dimethyl-1-phenylthiochromeno[2,3-c]pyrazol-4(1H)-one 123 (Scheme 43).

\textbf{Scheme 43.} Synthesis of phenylthiochromeno[2,3-c]pyrazol-4(1H)-one 123.

2.2.9. Fused [6-7-5] system with two heteroatoms. 4.2.9.1. Benzo[6,7]cyclohepta[1,2-c]pyrazole. El-Aal et al.\textsuperscript{88} reported that acrylic acids 126a and 126b were obtained by heating of pyrazole-4-carbaldehyde 4 with acid anhydride 124 and 125 and sodium salt of the corresponding acid, respectively. Subsequent reduction of 126a and 126b with sodium amalgam gave propanoic acid derivatives 127a and 127b which underwent esterification upon treatment with ethanol in the presence of sulfuric acid to give ethyl propanoate derivatives 128a and 128b. The reaction of Grignard reagent CH\textsubscript{3}MgI in ether with esters 128a and 128b gave 4-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)-2,3-dimethylbutan-2-ols 129a and 129b. Cyclization of compounds 129a and 129b by a Friedel–Crafts-type ring closure afforded benzo[6,7]cyclohepta[1,2-c]pyrazole derivatives 130a and 130b, respectively (Scheme 44).

\textbf{Scheme 44.} Synthesis of benzo[6,7]cyclohepta[1,2-c]pyrazole derivatives 130.
2.3. Pyrazole fused within a tricyclic system

2.3.1. Fused [6-5-6-6] system with three heteroatoms. 2.3.1.1. Benzo[h]pyrazolo[3,4-b]quinoline. Zheng et al.\textsuperscript{56} reported that a one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes \textbf{11} with 1-tetralone \textbf{131} in a solution of ethanolic KOH afforded the corresponding 10-phenyl-6,10-dihydro-5\textit{H}-benzo[h]pyrazolo[3,4-b]quinolines \textbf{132} (Scheme 45).

\begin{equation}
\text{Ph} \quad \text{N} \quad \text{N} \quad \text{R}^1 \\
\text{N} \quad \text{N} \quad \text{CHO} \\
\begin{array}{c}
\text{11} \\
\end{array}
\begin{array}{c}
\text{KOH-EtOH} \\
\text{Reflux} \\
\end{array}
\begin{array}{c}
\text{R}^1 = \text{CH}_3, \text{C}_6\text{H}_5. \\
\text{132} \\
\end{array}
\end{equation}

\textbf{Scheme 45.} Synthesis of 10-phenyl-6,10-dihydro-5\textit{H}-benzo[h]pyrazolo[3,4-b]quinolines \textbf{132}.

Jachak et al.\textsuperscript{70} reported that the cyclocondensation of \textbf{11} with 6-methoxy-1-tetralone \textbf{131} yielded benzo[h]pyrazolo[3,4-b]quinolines \textbf{133} in moderate yields (Scheme 46).

\begin{equation}
\text{Ph} \quad \text{N} \quad \text{N} \quad \text{Ar} \\
\text{N} \quad \text{N} \quad \text{NH}_2 \\
\begin{array}{c}
\text{11} \\
\end{array}
\begin{array}{c}
\text{H}_3\text{C} - \text{O} \\
\text{131} \\
\end{array}
\begin{array}{c}
\text{KOH} \\
\text{EtOH} \\
\text{1 h, reflux} \\
\end{array}
\begin{array}{c}
\text{Ar} = 4-\text{Cl-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4. \\
\text{133} \\
\end{array}
\end{equation}

\textbf{Scheme 46.} Synthesis of benzo[h]pyrazolo[3,4-b]quinolines \textbf{133}.

2.3.1.2. Benzo[h]pyrazolo[4,3-c]isoquinolin. Vovk et al.\textsuperscript{95} reported that treatment of 4-formyl-3-(2-naphthyl)-3-(naphthalen-2-yl)-1-phenyl-1\textit{H}-pyrazole-4-carbaldehyde \textbf{1} with potassium permanganate afforded 3-(2-naphthyl)-1-phenylpyrazole-4-carboxylic acid \textbf{83}. Heating of compound \textbf{83} with thionyl chloride and drops of DMF followed by treatment of the acid chloride formed with trimethylsilyl azide in toluene afforded 4-isocyanato-3-(2-naphthyl)-1-phenylpyrazole \textbf{134}. When a solution of \textbf{134} in \textit{o}-dichlorobenzene was added to a suspension of \textit{AlCl}_3 in \textit{o}-dichlorobenzene, 2-phenyl-2\textit{H}-benzo[h]pyrazolo[4,3-c]isoquinolin-10(11\textit{H})-one \textbf{135} was obtained in good yield (Scheme 47).
Scheme 47. Synthesis of 2H-benzo[h]pyrazolo[4,3-c]isoquinolin-10(11H)-one 135

2.3.2. Fused [6-6-5-6] system with three heteroatoms. 2.3.2.1. Benzopyrano[4',3'-e]pyrazolo[3,4-b]pyridine. Sabitha et al.\textsuperscript{59} reported that the condensation of 5-amino-1-phenyl-1H-pyrazole-4-carbaldehyde 11 with 4-chromanone 136 at reflux in ethanol in the presence of a catalytic amount of piperidine gave 8-phenyl-6,8-dihydrochromeno[4,3-b]pyrazolo[3,4-e]pyridines 137. Also, when 5-chloro-1-phenyl-1H-pyrazole-4-carbaldehyde 4 was treated with 4-chromanone 136 in NaOEt/EtOH at room temperature it gave the 8-phenyl-6,8-dihydrochromeno[4,3-b]pyrazolo[3,4-e]pyridines 137 via the intermediacy of 138 by heating in AcOH with NH\textsubscript{4}OAc (Scheme 48).


2.3.3. Fused [6-6-5-6] system with two heteroatoms. 2.3.3.1. Naphtho[1,8-fg]indazole. Naphthyl-substituted pyrazole 1 undergo intramolecular Friedel–Crafts-type reactions to afforded 9-phenylnaphtho[1,8-fg]indazol-7(9H)-one 139 and 9-phenyl-7,9-dihydronaphtho[1,8-fg]indazole 140 in roughly equimolar amounts via reaction with trifluoromethanesulfonic acid (CF\textsubscript{3}SO\textsubscript{3}H)\textsuperscript{96} as Brønsted acid (Scheme 49).
Scheme 49. Synthesis of naphtho[1,8-fg]indazolone 139 and 7,9-dihydronaphtho[1,8-fg]indazole 140.

2.3.4. Fused [6-6-6-5] system with four heteroatoms. 2.3.4.1. Pyrano[3′,2′:6,7]chromeno[4,3-c]pyrazole. Ajay et al.\textsuperscript{97} reported that pyrano[3′,2′:6,7]chromeno[4,3-c]pyrazoles 141 and pyrano[2′,3′:5,6]chromeno[4,3-c]pyrazoles 142 were synthesized by the cyclocondensation reaction of 3,3′-(7-hydroxy-4-methyl-2-oxo-2H-chromene-6,8-diyl)bis(1-aryl-1H-pyrazole-4-carbaldehydes) 1 in ethyl alcohol in the presence of conc. H\textsubscript{2}SO\textsubscript{4} under reflux conditions (Scheme 50).


Conclusions

Nitrogen-based heterocyclic chemistry is a special and significant branch of organic chemistry that has recently gotten a lot of attention. There has been a lot of emphasis on developing new structures for this class of molecules. N-heterocyclic compounds' pharmacological properties have been reported.

They are components of a wide range of biologically important naturally occurring compounds. Due to their broad range of applications, pyrazole derivatives are one of the most active groups of five-member heterocycles among the various nitrogen-containing heterocycles. The utility of pyrazole-4-carbaldehydes as precursors for the preparation of pyrazole-fused heterocyclic systems over the last two decades was highlighted in this study. Our group recently reviewed various synthetic methods for the preparation of pyrazole-4-carbaldehydes and their utility as versatile precursors for various pyrazole-substituted heterocyclic systems as hybrid molecules. The heterocyclic compounds discussed in this review are categorized according
to the size of the heterocyclic ring, as well as the position and number of heteroatoms. We hope that this study will be useful to researchers interested in medicinal chemistry as well as synthetic organic chemists.

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Ismail A. Abdelhamid was born in Egypt in December 1978. He graduated from Cairo University, Egypt in 2001 then he got his M.Sc. and Ph.D. degrees in 2005 and 2007, respectively, at Cairo University in the field of organic synthesis. In 2017 he was appointed as a full Professor of Organic chemistry at Cairo University. He was awarded the Alexander von Humboldt research fellowship in 2008–2011 and in 2014, 2017, and 2019 with Prof. Holger Butenschôn, at Hannover University, Germany. He received several research prizes; Cairo University Incentive Award (2012), Cairo University Scientific Excellence Award (2016) and State Incentive Award (2019).

Mahmoud A. E. Hawass was born in 1985 in Giza, Egypt. He has graduated from Cairo University, Faculty of Science, Egypt in 2008 then he got his M.Sc degree in 2014. He has published four paper in the field of organic synthesis.
Sherif M. H. Sanad was born in Egypt in July 1980. He graduated from Cairo University, Egypt in 2002 then he got his M.Sc. and Ph.D. degrees in 2009 and 2012, respectively, at Cairo University in the field of organic synthesis. In 2019 he was appointed as associated professor of Organic chemistry at Cairo University.

Ahmed H. M. Elwahy was born in 1963 in Giza, Egypt. He graduated from Cairo University, Egypt in 1984 then he got his M.Sc. and Ph.D. degrees in 1988 and 1991, respectively, at Cairo University in the field of organic synthesis. He was awarded the Alexander von Humboldt research fellowship in 1998–2000 and in 2003, 2005, 2009, 2010 and 2012 with Prof. Klaus Hafner, at TU Darmstadt, Germany. In 2002 he was appointed as a full Professor of Organic chemistry at Cairo University. In 2001 he received the State-Award in Chemistry and in 2016 received Cairo University Appreciation-Award in Basic Science. He published around 140 scientific papers in distinguished international journals.

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