Pyrazole-3(4)-carbaldehyde: synthesis, reactions and biological activity

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Abstract
This review deals with synthesis and reactions of pyrazole-3(4)-carbaldehydes as well as their biological activity. The data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last years are reviewed here for the first time.

Keywords: Vilsmeier-Haack reaction, phenylhydrazone, pyrazolecarbaldehyde, chalcone, hydroxyalkylation

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1. Introduction

A literature survey revealed that a number of biologically active compounds have been synthesized using pyrazole-3(4)-carbaldehydes. These compounds show antimicrobial,\(^1\)-\(^3\) anti-inflammatory (COX-2 inhibitor and ulcerogenic activity),\(^3\) antitubercular,\(^4\) antitumor,\(^5,6\) antiangiogenesis,\(^6\) anti-parasitic,\(^7\) and antiviral activity.\(^8\) Despite this versatile importance, pyrazole-3(4)-carbaldehydes have not been previously reviewed. This review is not exhaustive; it is intended to get the reader acquainted with interesting group of synthetic organic compounds. It is the objective of this review to summarize the synthesis, the chemical reactions, and biological activity of pyrazole-3(4)-carbaldehydes till the end of 2010 and provide useful and up-to-date data for organic chemists.

2. Synthetic Methods

There have been a number of practically important routes to synthesise of pyrazole-3(4)-carbaldehydes, e.g. (i) Vilsmeier-Haack reaction of hydrazones, (ii) oxidation of the corresponding alcohols, and (iii) miscellaneous methods.

2.1. Vilsmeier-Haack reaction

3-Aryl(alkyl)-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were obtained via the Vilsmeier-Haack reaction of the appropriate phenylhydrazones 2, derived from the reaction of aryl methyl ketone 1 with phenylhydrazine (Scheme 1).\(^7,9-16\)

![Scheme 1](image-url)
3-Substituted pyrazole-4-carbaldehyde 5 was prepared by formylation of semicarbazones 4, derived from alkyl, phenyl, and cycloalkyl methyl ketones, with the complex of POCl₃ with dimethylformamide (Scheme 2).

\[
\begin{align*}
&\text{R} = \text{Ph, C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{n-C}_4\text{H}_9, \text{CH}_2\text{CH(CH}_3)_2, \text{CH(CH}_3)_2, \text{cyclohexyl}
\end{align*}
\]

Scheme 2

Salicylaldehyde (6, R = H) and 2-hydroxyacetophenone (6, R = Me) on reaction with chloroacetone 7 afforded the corresponding 2-acetylbenzofuran (8, R = H) and 2-acetyl-3-methylbenzofuran (8, R = Me) respectively. Compounds 8 on treatment with arylhydrazine in ethanol gave phenylhydrazones 9 which underwent cyclization with DMF/POCl₃ to produce substituted pyrazoles 10 (Scheme 3).

\[
\begin{align*}
&\text{R} = \text{H, CH}_3; \text{Ar} = \text{Ph}, \text{4-NO}_2\text{C}_6\text{H}_4, \text{4-OCH}_3\text{C}_6\text{H}_4
\end{align*}
\]

Scheme 3

A variety of 3-Aryl(alkyl)-1-phenyl-1H-pyrazole-4-carbaldehydes 3 can be prepared in good yields from the corresponding methyl ketone hydrazones 2, upon treatment with 2,4,6-trichloro[1,3,5]triazine in N,N-dimethyl formamide at room temperature (Scheme 4).
Ramu, and Rajagopal have been reported the synthesis of 3,6-di(pyrazol-4-yl)carbazoles 13. The reaction of the Vilsmeier reagent with hydrazones of diacetylcarbazoles 12 yielded the corresponding pyrazole dicarbaldehydes 13 in good yields (Scheme 5).\textsuperscript{19}

Scheme 4

Scheme 5

2,6-Dichloro-4-trifluoromethylphenylhydrazine 15 was synthesized from amine 14 through diazotization, followed by reduction using SnCl\textsubscript{2}/HCl. Phenylhydrazones 16 were next
synthesized in almost quantitative yields by the reaction between the phenylhydrazine 15 and aryl methyl ketones. When hydrazones 16 reacted with three equivalents of Vilsmeier reagent at 80-90 °C for 4 h gave 1-[(2,6-dichloro-4-trifluoromethyl)phenyl]-3-aryl-1H-pyrazole-4-carbaldehydes 17 in good yields (Scheme 6). \(^{20}\)

\[ \text{Scheme 6} \]

\[ N,N\text{-Disubstituted-}N\text{-[1,3-diphenyl-4-formyl-1H-pyrazol-5-yl]formimidamides 19 were synthesized by microwave irradiation of 5-amino-1,3-diphenyl-1H-pyrazole 18 with various amide solvents in the presence of POCl}_3. \text{The obtained formimidamides 19, showed anticancer activity (Scheme 7).}^{21} \]
It was reported the synthesis of 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1H-pyrazole-4-carbaldehyde 22, using Vilsmeier Haack complex from \( N' \)-[1-(4-nitrophenyl)ethylidene]benzohydrazide 21, which was prepared from reaction of 4-nitroacetophenone 1 and hydrazide 20, in the presence of acetic acid. Pyrazolylthiazolidin-4-one 23, has been synthesized by the reaction of pyrazole-4-carbaldehyde 22, with 2-mercaptoacetic acid and different substituted aromatic amines in toluene (Scheme 8).

\[
\begin{array}{c|c|c|c}
\text{No} & R^1 & R^2 & R^3 \\
19a & H & Et & Et \\
19b & H & Pyrrolidinyl & \\
19c & H & Piperidinyl & \\
19d & H & H & Me \\
19e & Me & H & Me \\
19f & Et & H & Me \\
19g & Me & Me & Me \\
19h & Ph & Me & Me \\
19i & Et & Me & Me \\
\end{array}
\]

\[\text{Scheme 8}\]

\[
\begin{align*}
\text{R}^1 &= 4-\text{NO}_2\text{C}_6\text{H}_4; \text{R}^1 = 4-\text{Pyridyl}; \text{R}^2 = \text{Ph}, 4-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, \\
&\quad 3-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4.
\end{align*}
\]

\[\text{Scheme 8}\]
1-Ethylpyrazole-4-carbaldehyde 24, 1-ethyl-3,5-dimethylpyrazole-4-carbaldehyde 25, and 1,1'-methylenebis(3,5-dimethylpyrazole-4-carbaldehyde) 26, were synthesized from the corresponding N-alkylpyrazoles by the Vilsmeier-Haack reaction (Figure 1).23

Figure 1

Ethyl 2-(arylamidrazono)propanoates 27, were reacted with the Vilsmeier-Haack reagent to give ethyl 1-aryl-4-formyl-1H-pyrazole-3-carboxylates 28. Reactions of pyrazole derivatives with hydrazine and methylhydrazine led to the formation of the corresponding 2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-ones 29 (Scheme 9).24,25

Scheme 9

Formylation of 3,5-dimethyl-1H-pyrazoles (30, R = alkyl) according to Vilsmeier-Haack, by using phosphoryl chloride in DMF at 90-120 °C, led to the formation of the corresponding 4-formyl derivatives 31. In contrast, 3,5-dimethyl-1H-pyrazole (30, R = H) failed to undergo formylation at the position 4 under analogous conditions. It is presumed that electrophilic substitution in the molecule (30, R = H) occurs at the nitrogen atom to give ammonium ion, which hampers formylation at the 4 position. The formyl group in 3,5-dimethyl-1H-pyrazole-4-carbaldehyde is extremely labile and is readily eliminated by the action of basic reagents (NaOH). 3,5-Dimethyl-1H-pyrazole-4-carbaldehyde 35 was synthesized by reaction of (30, R = H) with methyl acrylate followed by reaction with POCl3/DMF followed by alkaline hydrolysis of methyl β-(4-formyl-3,5-dimethyl-1H-pyrazol-1-yl)propionate 33 and subsequent heating of the acid 34 formed (Scheme 10).26
1-(2-Hydroxyethyl)-3,5-dimethyl-1H-pyrazole 36 does not undergo Vilsmeier–Haack formylation and substitution of the hydroxyl group in the 2-hydroxyethyl moiety by chlorine atom to form compound 40. The reaction of N-chloroethylpyrazole 40 with Vilsmeier reagent afforded N-chloroethylpyrazole-4-carbaldehyde 41. Synthesis of 1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazole-4-carbaldehyde 39 took place by acylation of 36 with acetic anhydride to give acylated product 37, which readily underwent Vilsmeier-Haack formylation to give 38 followed by hydrolysis as described in Scheme 11.\(^{27}\)
5-Chloro-1-phenyl-3-pyridin-4-yl-1H-pyrazole-4-carbaldehyde 43 was obtained by the reaction of 2-phenyl-5-pyridin-4-yl-2,4-dihydropyrazol-3-one 42 with dimethylformamide and phosphorus oxychloride under Vilsmeier-Haack reaction conditions (Scheme 12).\(^{28}\)

\[
\begin{align*}
\text{R} = 4\text{-Pyridyl}; \text{Ar} = \text{Ph}, 4\text{-CH}_2\text{C}_6\text{H}_4
\end{align*}
\]

Scheme 12

Ethyl 1-(2,4-dinitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate 45 was prepared in 15% yield from 2,4-dinitrophenylhydrazone 44 by treatment with 8 equivalents of POCl\(_3\) (Scheme 13), which has antibacterial activity against E. coli, S. aureus, En. Faecalis and P. aeruginosa.\(^{29}\)

\[
\begin{align*}
\text{Me} & \text{NN} \rightarrow \text{O}_2\text{N} & \text{N} \rightarrow \text{C}_2\text{Et} \\
\text{CHO} & \rightarrow \text{CHO} \\
\text{DMF, POCl}_3 & \rightarrow \text{DMF, POCl}_3 \\
\text{70-80 °C, 4 h} & \rightarrow \text{70-80 °C, 4 h}
\end{align*}
\]

Scheme 13

Arylhydrazones of dehydroacetic acid (DHA) 46 underwent Vilsmeier-Haack reaction to generate the corresponding 3-(4-hydroxy-2-oxo-6-aryl-2H-pyran-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes 48. However, when the reaction was performed using one equivalent of Vilsmeier reagent, 3-(pyran-2-on-3-yl)pyrazoles 47 were obtained, which underwent smooth conversion to 48 on further treatment with another equivalent of the Vilsmeier-Haack reagent (Scheme 14).\(^{30}\)
2.2. Oxidation of the corresponding alcohols

1,3-Diaryl-1H-pyrazole-4-carbaldehydes 3 were prepared by oxidation of the corresponding (1,3-diaryl-1H-pyrazol-4-yl)methanol 49 in 50-85% yields by FeCl₃.6H₂O catalyzed by a free radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). This reaction gave high yield of the corresponding aldehydes with no over oxidation to carboxylic acids (Scheme 15).³¹

Treatment of acetophenones 1 with diethyl oxalate in the presence of NaH furnished the diketoesters 50. Reaction of 50 with phenylhydrazine in the presence of catalytic amount of TFA yielded a mixture of pyrazole esters 51 and 52. The mixture containing both regioisomers was treated with LiAlH₄ in dry diethyl ether to afford the product as a mixture of 53 and 54. Due to significant difference in the polarity of these alcohols, they were easily separated via column chromatography over silica gel. Compounds 53 were obtained as the major isomer while 54 were separated as the minor product. Subsequently, these alcohols 53 and 54 were subjected to oxidation in the presence of PCC, affording 1,5-disubstituted-1H-pyrazole-3-carbaldehyde 55 and 1,3-disubstituted-2H-pyrazole-5-carbaldehyde in 55-57% and 75-80% yields, respectively (Scheme 16).⁹
Scheme 16

Claisen condensation of acetyl ferrocene 57 and diethyl oxalate in the presence of NaOEt was reported to furnish ethyl 2,4-dioxo-4-ferrocenylbutanoate 58 in 52% yield. Esters of 1-aryl-5-ferrocenyl-1H-pyrazole-3-carboxylic acids 59 were synthesized in high yields by the condensation between ethyl 2,4-dioxo-4-ferrocenylbutanoate 58 (enol form) and arylhydrazines in boiling ethanol in the presence of a catalytic amount of acetic acid. The corresponding alcohols 60 were obtained by reduction of esters 59 with LiAlH₄ in a mixture of THF and 1,4-dioxane. Oxidation with MnO₂ in CH₂Cl₂ at room temperature led to the formation of aldehyde 61 (Scheme 17).³²

Scheme 17
Pyridyl-2,4-dioxo-butanoate 62 was reacted with 4-(methylsulfonyl)phenylhydrazine in methanol at reflux temperature to afford 63. The ester group in 63 was reduced with DIBAL-H to give the corresponding hydroxymethyl-(3-pyridyl)pyrazole derivative 64. The oxidation of 64 with pyridinium chlorochromate afforded (3-pyridyl)pyrazole-4-carbaldehyde 65 (Scheme 18).\(^{33}\)

Scheme 18

2.3. Miscellaneous Methods

5-Amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(methylsulfinyl)-1H-pyrazole-3-carbonitrile 66 was reduced to the corresponding aldehyde 67 using (iso-Bu)$_2$AlH. Pyrazole-3-carbaldehyde 67 was converted to oxime 68 with hydroxylamine.HCl in pyridine (Scheme 19).\(^{34}\)

Scheme 19
Hydrolysis of 4-arylaminomethyl-3-trimethylsilylpyrazoles 70, obtained by the reaction of $\alpha,\beta$-acetylenic aldimines 69 with diazomethane, afforded 3-trimethylsilyl-1,2-pyrazole-4-carbaldehyde 71 in a good yield (Scheme 20).  

![Scheme 20](image)

3. Chemical Reactions

3.1. Addition and reduction

1,3-Diarylpyrazol-4-ylacetic acids 72, which are known antiinflammatories and thrombocyte aggregation inhibitors, are prepared by reaction of 1,3-diaryl-1H-pyrazole-4-carbaldehydes 3 with $\geq 1.2$ equiv of HCN (prepared in situ from NaCN or KCN and an organic or inorganic acid) in a polar solvent (DMF, 2-PrOH, 2-BuOH) at 5-40 °C, to give aldehyde cyanohydrin and then reduction with 1 equiv of SnCl$_2$ in HCl-AcOH (Scheme 21).

![Scheme 21](image)

Cyanohydrins of pyrazolecarbaldehydes 73 were prepared as intermediates for inflammation inhibitors by a safer method comprising reaction of the parent 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with $\geq 1.2$ equiv of HCN (Scheme 22).
3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were reduced with sodium borohydride under mild conditions to give hydroxymethylpyrazoles 74 which were converted into the corresponding 4-chloromethyl derivatives 75 by treatment with thionyl chloride. The subsequent reaction with triphenylphosphine led to the formation of triphenyl(4-pyrazolylmethyl)phosphonium chlorides 76, and Wittig reaction of the latter with aromatic or heteroaromatic aldehydes yielded 4-[2-arylethenyl]pyrazoles 77 (Scheme 23).
3.2. Oxidation

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde 43 was subjected to oxidation with potassium permanganate to afford pyrazole-4-carboxylic acid 78, which converted to the corresponding ethyl ester 79 by reaction with ethanol in acidic medium (Scheme 24).²⁸

![Scheme 24](image)

R = 4-pyridyl

**Scheme 24**

3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were cleanly oxidized by potassium permanganate in water-pyridine medium to afford the corresponding acids 80 in high yield, these were further converted into the corresponding chlorides 81 and amides 82 as depicted in Scheme 25.³⁹

![Scheme 25](image)

**Scheme 25**

Abu-Zaied et al., reported the synthesis of pyrazolyloxadiazoles 86. Thus, 3-substituted-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were converted to 1,3,4-oxadiazole derivatives 84 by oxidation using acidic K₂Cr₂O₇ followed by esterification to pyrazole esters 83, which reacted with hydrazine to give hydrazides 84. Finally, compounds 84 were converted to pyrazolyloxadiazole 85 when reacted with carbon disulphide in KOH solution. Pyrazolyloxadiazoles 85 reacted with alkyl bromides or halosugars in the presence of basic medium to produce alkylated adducts 86 (Scheme 26).¹³
3.3. Condensation reactions

3.3.1. Reactions with active methylene compounds. 1,3,5,6-Tetrasubstituted pyrazolo[3,4-b]pyridines 88-91 have been synthesized by Friedländer condensation of 5-aminopyrazole-4-carbaldehydes 87, with active methylene compounds such as ketones, malononitrile, phenyl acetonitrile, and cyanoacetamide, respectively, in alcoholic potassium hydroxide as a basic catalyst (Scheme 27). 40-42
3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 underwent aldol condensation reactions with methyl ketones to give diaryl pyrazolylpropenones 92. Chalcones 92 underwent cyclocondensation with phenylhydrazine to give pyrazolyl pyrazoline derivatives 93 useful as potential components of luminescent composite dyes (Scheme 28).
5-Chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde 43 was allowed to react with different reagents such as aromatic ketones and hippuric acid to afford $\alpha,\beta$-unsaturated ketones 94, and 5-oxazolones 95, respectively (Scheme 29).

\[
\begin{align*}
\text{R} = 4\text{-pyridyl}; \text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4 \\
\end{align*}
\]

Scheme 29

2,4-Dichloro-5-fluoroacetophenone 96 was reacted with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 to give 1-(2,4-dichloro-5-fluorophenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one 97 (Scheme 30).

\[
\begin{align*}
\end{align*}
\]

Scheme 30

The reaction of 1,3-diaryl-1H-pyrazole-4-carbaldehydes 3 with various substituted acetophenones in methanol in the presence of EtONa gave the corresponding $\alpha,\beta$-unsaturated ketones 98 in good yields. Refluxing 98 with different phenacyl pyridium bromides in acetic acid in the presence of ammonium acetate under Krohnke's conditions gave pyridinylpyrazoles 100 in good yields (Scheme 31).
Scheme 31

2-Aminopyrimidothiazolo[4,5-b]quinoxalin-4-one 102 was utilized as a key intermediate for the synthesis of pyrimidothiazolo[4,5-b]quinoxaline derivatives 103 via reaction with 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 101 in acetic acid at reflux temperature (Scheme 32).\(^\text{46}\)

Scheme 32

Condensation of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with malonic acid furnished 3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)propenoic acids 104, which in the presence of Raney nickel reduced to the corresponding propanoic acids 105. The successive conversion of both type acids into the corresponding acyl chlorides, was performed by reaction with thionyl chloride (Scheme 33).\(^\text{47}\)

The reaction of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile and 2-(1H-benzo[d]imidazol-2-yl)acetonitrile with 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehydes 101 in ethanol or dioxane gave the corresponding quinazolyl-2-propenenitrile 104 and benzimidazolyl-2-propenenitrile 106, respectively. Intramolecular cyclization of the latter compounds in DMF in the presence of Et,N afforded pyrazolo[3,4-b]pyrido[2,1-b]quinazoline-5-carbonitrile 105, and benzo[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyridine-5-carbonitrile 107, respectively (Scheme 34).\(^\text{48}\)
Condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 with 2-cyanomethyl-4-thiazolinone 108 in ethanol containing a few drops of piperidine yielded methylene derivative 109 (Scheme 35).
Scheme 35

Oximes of 4-(4-pyrazolyl)-3-buten-2-ones 110, obtained by successive reaction of 3 with acetone and hydroxylamine, upon treatment with iodine suffered an oxidative cyclization, yielding 4-(5-isoaxazolyl)pyrazoles 111 (Scheme 36).\(^{50}\)

\[
\begin{align*}
\text{Ph} & \quad \text{CHO} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{3} \\
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{CN} \\
\text{EtOH/Pip.} & \quad \text{108} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{109} \\
\end{align*}
\]

\[\text{Ar}^1 = \text{Ph, 4-FC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{EtC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4\]

Scheme 36

Pyrazole-4-carbaldehyde 3 was reacted with 2-hydroxyacetophenone 112 in methanol in the presence of KOH to give chalcone 113. Oxidation of 113 with hydrogen peroxide (H\(_2\)O\(_2\)) in KOH/MeOH afforded 2-(3-aryl-1-phenyl-1\(H\)-pyrazol-4-yl)-4\(H\)-chromen-4-ones 114 in high yields, these compounds showed antifungal activity (Scheme 37).\(^{51,52}\)

\[
\begin{align*}
\text{OH} & \quad \text{Me} \\
\text{KOH} & \quad \text{MeOH} \\
\text{Ar} & \quad \text{CHO} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{3} \\
\text{112} & \quad \text{113} \\
\text{H}_2\text{O}_2 & \quad \text{KOH, MeOH} \\
\end{align*}
\]

\[\text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4\]

Scheme 37
Base-catalyzed condensation of 5-fluoro-2-hydroxyacetophenone 115 with 3-aryl-1-phenyl-1H-pyrazol-4-carbaldehyde 3, gave 1-(5-fluoro-2-hydroxyphenyl)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-ones 116. On oxidative cyclization with DMSO-CuCl$_2$, 116 gave 2-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-3-chloro-6-fluorochromones 117. On cyclization with DMSO-I$_2$, 116 gave 2-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-fluorochromones 118. When 116 was heated with N$_2$H$_4$ in dioxane, 5-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-3-(5-fluoro-2-hydroxyphenyl)-4,5-dihydropyrazolines 119 was formed. These compounds exhibited moderate antibacterial and moderate to high antifungal activities (Scheme 38).

Scheme 38

Condensation of substituted 2-hydroxyacetophenones 120 with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 produced the pyrazolylpropenones 121, which on oxidative cyclization with DMSO/CuCl$_2$ gave the (diphenyl-1H-pyrazol-4-yl)chlorochromone 122. Condensation of 121 with 2-aminothiophenol gave the benzothiazepines 123 (Scheme 39).
Chalcones 124 were synthesized by reaction of 3 with derivatives of aryl methyl ketone. Condensation of 124 with barbituric acid in the presence of acetic acid afford Barbitones 125 (Scheme 40).
4-Pyrazolyl-4H-pyrazolopyran 129, 4-pyrazolyltetrahydrochromene-3-carbonitrile 130, and 4-pyrazolynaphthopyrans 131 and 132 were synthesized by one-pot base-catalyzed cyclocondensation reactions of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3, malononitrile, with substituted pyrazolin-5-ones 126, dimedone 127, or naphthols 128a,b, respectively (Scheme 41). Some of these compounds tested as antimicrobial.56

![Pyrazolylacrylic acids and pyrazolylmethylenemalonic acids](image)

**Scheme 41**

Pyrazolylacrylic acids 134 and pyrazolylmethylenemalonic acids 133 were prepared by the Knoevenagel condensation of 1,3-diaryl-1H-pyrazole-4-carbaldehydes 3 with malonic acid or ester (Scheme 42). Some of these compounds showed anti-inflammatory activity and were less active, but less toxic than phenylbutazone.57
Under microwave activation, 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 reacted with malonic acid in the presence of a small amount of pyridine to give 3-(4-pyrazolyl)propenoic acids 134 in high yields (Scheme 43).

A simple and rapid synthesis of 3-(1,3-diaryl-1H-pyrazol-4-yl)propanoic acids 136 using Meldrum’s acid 135 from the corresponding aldehydes 3 was reported (Scheme 44).
Knoevenagel condensation of 1,3-diphenyl-1H-pyrazol-4-carbaldehyde 3 has been carried out with 3-methyl-1-phenylpyrazolin-5-(4H)-one 137 as condensing agent was carried out to give 4-pyrazolylmethylenepyrazol-5-one 138, using Borate Zirconia (B_2O_3/ZrO_2) solid acid catalyst in aqueous medium\(^6^0\) or an ionic liquid (ethylammonium nitrate) at room temperature (Scheme 45).\(^6^1\) In each conversion, the catalyst was successfully recovered and recycled without significant loss in yield and selectivity. On the other hand these compounds were synthesized by traditional, microwave, and ultrasonic irradiations.\(^6^2-6^7\)

![Scheme 45](image)

Pyrazolylmethyleneoxazolones 139 were prepared by condensation of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with acylglycine and hydrolysed to give 3-aryl-1-phenyl-4-pyrazolopyruvic acids 140. These were converted to pyrazole-4-acetic acids 72 and pyrazole-4-acetonitriles 141 by oxidative decarboxylation using H_2O_2 and reaction with a mixture of hydroxylamine and acetic anhydride, respectively (Scheme 46).\(^6^8,6^9\)
Reactions of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with various reagents, such as benzyolglycine, and ethyl azidoacetate, gave 4-(4-pyrazolidene)-1,3-oxazol-5-ones 139, and pyrrolopyrazoles 143, respectively. Treatment of 139 with hydrazine afford the corresponding hydrazides 142 (Scheme 47). 70, 71

Scheme 46

\[
\begin{align*}
R & = \text{Ph, 4-ClC}_6\text{H}_4, 2\text{-thienyl; } R^1 = \text{Me, Ph} \\
\end{align*}
\]

Scheme 47

\[
\begin{align*}
R & = \text{Ph, 4-BrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-thienyl} \\
\end{align*}
\]
Biginelli coupling reaction of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with ethyl acetoacetate and urea (thiourea) in the presence of FeCl₃.6H₂O, phosphotungstic acid or a Keggin's type heteropoly acid afforded 4-(3-aryl-4-pyrazolyl)-1,2,3,4-tetrahydropyrimidin-2-ones (thiones) 144 (Scheme 48).

![Scheme 48](image)

Ar = Ph, 4-CIC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄, 2-thienyl
X = O, S

**Scheme 48**

1,3-Diphenyl-1H-pyrazole-4-carbaldehyde 3 was reacted with ethyl cyanoacetate and thiourea to give the pyrimidinethione 145 (Scheme 49).

![Scheme 49](image)

**Scheme 49**

The Knoevenagel condensation of N-(benzothiazol-2-yl)-2-cyanoacetamide 146 with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 in ethanolic sodium hydroxide (10%) afforded N-(benzothiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide 147, and then addition of hydrazine hydrate to the activated double bond of the compound 147 in boiling ethanol afforded 5-amino-N-(benzothiazol-2-yl)-1,3-diphenyl-1H,1H-3,4-bipyrrole-4-carboxamide 148. In addition, the condensation of 5-amino-N-(benzo[d]thiazol-2-yl)-3-(phenylamino)-1H-pyrazole-4-carboxamide 149 with 3 in boiling ethanol in the presence of a catalytic amount of piperidine furnished the corresponding Schiff’s base 150 in an excellent yield (Scheme 50).
Cyanoacetylhydrazine was reacted with 4-acetyl-5-methyl-2-phenylimidazole 151 to give the hydrazide-hydrazone derivative 152. The reaction of 152 with 3-heteroyl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 and 10 gave the knoevenagel adducts 153 in high yields (Scheme 51).

3, R = 2-thienyl; 10, R = 2-benzofuryl
Knoevenagel condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehydes 3 with barbituric acid (154, X = O), thiobarbituric acid (154, X = S) in glacial AcOH gave the condensation products 155. The synthesized barbitones (155, X = O) and thiobarbitones (155, X = S) showed antibacterial and antifungal activities (Scheme 52).\(^{78}\)

\[\text{Scheme 52}\]

5-Aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3H)-furanones 157 were prepared by condensing 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 with 3-arylpionic acids 156 in the presence of \(N,N\)-dimethyl(chlorosulfinyloxy)methaniminium chloride as a cyclodehydrating agent (Scheme 53).\(^{79}\)

\[\text{Scheme 53}\]

The crotonic condensation of 3-acetylquinolones 158 with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 gave \(\alpha,\beta\)-unsaturated ketones 159 (Scheme 54).\(^{80}\)
Scheme 54

3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethyl-3-furanyl)prop-2-en-1-one 162 was synthesized in a high yield by an aldol condensation between 3-acetyl-2,5-dimethylfuran 161 and 3,5-dimethyl-1-phenylpyrazole-4-carbaldehyde 160 in ethanolic NaOH at room temperature (Scheme 55).81

Scheme 55

Cyclocondensation reaction of methyl 4-formyl-1-phenyl-1H-pyrazole-3-carboxylate 163 with methyl acetoacetate, and ethyl 3-aminocrotonate 164 in the presence of 3,4,5-trifluorobenzeneboronic acid, gave 3-ethyl 5-methyl 4-(3-methoxycarbonyl-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxilate 165 in 92% yield (Scheme 56).82
3.3.2. Reactions with semicarbazide, thiosemicarbazide, and hydroxylamine

1,3-Diphenyl-1H-pyrazole-4-carbaldehyde 3 was reacted with hydrazine, semicarbazide, thiosemicarbazide, or hydroxylamine affording the corresponding azomethines 166, 167, 168, and 169 respectively which have antibacterial and antifungal activities. On the other hand, the one-pot synthesis of hydrazone, semicarbazone, thiosemicarbazone, and oxime, derivatives of pyrazole-4-carbaldehydes 166-169 was accomplished by the Vilsmeier-Haack reaction of acetophenone phenylhydrazones 2 under a new workup procedure (i.e. treatment with hydrazine, semicarbazide, thiosemicarbazide, or hydroxylamine, followed by NaHCO₃) (Scheme 57).

A series of N-glycosyl-N'-pyrazolylmethyleneaminothioureas 171 was synthesized via condensation of N-glycosyl-N'-aminothioureas 170 with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 (Scheme 58).
Scheme 58

2,4-Disubstituted thiazole derivatives were synthesized by the reaction of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with thiosemicarbazide to give thiosemicarbazone 168. The latter compound underwent reaction with phenacyl bromide to give 2-(2-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)-4-phenylthiazole 172 which have antibacterial activity (Scheme 59).85

Scheme 59

Synthesis of 1,3-diaryl-4-cyanopyrazole 173 from the corresponding aldoxime 169 using dimethylformamide-thionyl chloride complex was reported (Scheme 60).86

Scheme 60
The pyrazole-4-carbaldehyde oximes 169 were prepared by one-pot procedure involving Vilsmeier-Haack reaction of acetophenonephenylhydrazones 2. Pyrazole-4-carbaldehyde oxime 169 was treated with iodobenzene diacetate (IBD, 1.1 equivalents) in dichloromethane at room temperature. A rapid reaction occurred and 3,4-bis(1,3-diphenylpyrazolyl)-1,2,5-oxadiazole-N-oxide 175 was obtained (Scheme 61).  

![Scheme 61](image)

R = Ph, 4-ClC₆H₄, 4-BrC₆H₄, 4-CH₃C₆H₄, 4-MeOC₆H₄, 4-NO₂C₆H₄

Scheme 61

Pyrazole-4-carbaldehyde-\(N,N\)-dimethylhydrazones 176, prepared by condensation of 3 with \(N,N\)-dimethylhydrazine, were reacted with the Vilsmeier-Haack reagent, followed by hydrolysis, and electrophilic substitution reaction took place at the azomethine C-atom, giving 2-hydrazone-2-(1\(H\)-pyrazole-4-yl)ethanals 177. Therefore, the electrophilic attack did not take place at the vinylogous position 5 of the pyrazoles (Scheme 62).  

![Scheme 62](image)

\( R^1 = \text{Ph}, 4-\text{CH₃C₆H₄}, 4-\text{MeOC₆H₄}, 4-\text{ClC₆H₄} \)

\( R^2 = \text{CH₃}, \text{Ph} \)

Scheme 62
3.3.3. Reactions with amines. Reduction of Schiff’s bases 178, derived from reaction of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with benzylamine, using sodium tetrahydroborate gave N-benzyl-1-(3-aryl-1-phenyl-1H-pyrazol-4-yl) methanamine 179 (Scheme 63).  

![Scheme 63](image)

One pot synthesis of 3-(pyrazol-4-yl)-benzo[f]quinolines (182, X = CH) and pyrazolyl-4,7-phenanthroline (182, X = N) in 39-55% yields was reported. Condensation of 3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde 3 with either 2-naphthylamine (180, X = CH) or 6-quinolylamine (180, X = N) and methyl ketones was performed in boiling ethanol in the presence of a catalytic quantity of hydrochloric acid. The aldehyde 3 was reacted with arylamine to give azomethine 181, after that, addition of the which added methyl ketones to the C=N bond of the azomethine, cyclocondensation of the arising amino-ketone s A gave into a dihydro derivatives of the azaphenanthrene B, and dehydrogenation of the latter into a completely aromatic 182 (Scheme 64).

The aldimine derivative,  N-(4-bromophenyl)-N-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene] amine, 183 was obtained in 60% yield from reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 3 with 4-bromoaniline. The aldimine derivative 183 and 1,3,5-tribromobenzene were dissolved in a mixture of DMF, electrolytic copper, KOH and 1,10-phenanthroline and the reaction mixture was heated for 15 h at 140 °C to give the 1,3,5-tris{[N-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-4-aminophenyl}benzene 184 (Scheme 65).
Scheme 64

\[
\text{3} + \text{180} \xrightarrow{\text{EtOH/HCl, reflux}} \text{181}
\]

\[
\xrightarrow{\text{CH}_3\text{COR}^1} \quad \text{A} \quad \xrightarrow{\text{R}^1}\quad \text{B}
\]

\[
\xrightarrow{\text{R} = \text{H}; \text{Ar} = 4-\text{FC}_{6}\text{H}_{4}; \text{R}^1 = \text{Me, Ph}; \text{X} = \text{CH, N}}
\]

Scheme 65
3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were functionalized at the 4-position by various substituted anilines, giving aldimines 185. The latter compounds have antibacterial, analgesic, and antianxiety activities (Scheme 66). \(^{7,10,91}\)

\[
\text{Ar} = 4-\text{ClC}_6\text{H}_4; \quad R = 4-\text{FC}_6\text{H}_4, 2-\text{MeC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4
\]

**Scheme 66**

1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazoles 188 have been given a great importance because of their special biological activities. Compounds 188 have been prepared through the intramolecular Mannich reaction of 4-amino-5-mercapto-1,2,4-triazoles 187 with 1-phenyl-3-methyl-5-chloropyrazole-4-carbaldehyde 186 as described in Scheme 67. \(^{92}\)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CHO} \\
\text{N} \quad \text{N} & \quad \text{Cl} \\
\text{Ph} &
\end{align*}
\begin{align*}
\text{HS} & \quad \text{N} \quad \text{N} \\
\text{NH}_2 & \quad \text{R}
\end{align*}
\begin{align*}
\text{R} & \quad \text{N} \quad \text{N} \\
\text{Cl} & \quad \text{N} \quad \text{N} \\
\text{H}_3\text{C} & \quad \text{Ph}
\end{align*}

R = alkyl, aryl

**Scheme 67**

When 3-isobutyl-1-phenyl-1H-pyrazole-4-carbaldehyde 3 was condensed with 4-amino-5-mercapto-1,2,4-triazoles 187 in ethanol in the presence of piperidine, the Schiff’s base adducts 189 were obtained in high yields. S-Glycosides 190 were obtained in fairly good yields, on treatment of compounds 189 with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in the presence of NaH/DMF (Scheme 68). \(^{13}\)
Pyrazolylbenzoxazoles 193 were synthesized by oxidative intramolecular cyclization of the corresponding Schiff’s bases 192, which was synthesized by reaction of 2-aminophenol 191 with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 in ethanol, by using iodobenzene diacetate in methanol (Scheme 69).
The reaction of 1-ethylpyrazole-4-carbaldehyde, 1-ethyl-3,5-dimethylpyrazole-4-carbaldehyde, and 1,1'-methylenbis(3,5-dimethylpyrazole-4-carbaldehyde) with primary amines (aniline, hydrazine, ethylenediamine, 1,4-phenylenediamine, and benzidine) gave the corresponding Schiff's bases 194-196, respectively (Figure 2).23

\[
\begin{align*}
\text{R}^1 &= \text{Ph, NH}_2, \text{CH}_2-\text{CH}_2-\text{NH}_2, 4-\text{NH}_2\text{C}_6\text{H}_4, \text{C}_6\text{H}_4-\text{C}_6\text{H}_4\text{NH}_2
\end{align*}
\]

**Figure 2**

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde 43 was allowed to react with sodium azide to afford 5-azidopyrazole-4-carbaldehyde 197, which was converted to pyrazolo[3,4-c]pyrazole 198 and pyrazolo[3,4-c]pyrazol-2(6H)-amine 199 by reaction with hydrazine in a mixture of ethanol and acetic acid at reflux temperature and in the presence of iodine at room temperature, respectively (Scheme 70).28

\[
\text{R} = 4-\text{pyridyl}
\]

**Scheme 70**

Ntramolecular [4+2] cycloaddition reactions of \(N\)-aryl imines generated \textit{in situ} from substituted aniline 200 and the \(S\)-allyl derivatives of pyrazole-4-carbaldehydes 201 was carried out in the presence of a catalytic amount of BiCl\(_3\) in acetonitrile to provide the corresponding hexahydropyrazolo[4',3':5,6]thiopyrano[4,3-b]quinolines 202 in excellent yields. The reactions are highly diastereoselective and the \textit{cis} products are exclusively isolated (Scheme 71).94
3.4. Friedel–Crafts-type reaction (Hydroxyalkylation)

Aldehydes were reacted in the Brønsted superacid, triflic acid (CF$_3$SO$_2$H, TfOH), to generate electrophilic intermediates capable of reacting with an arene in condensation reactions. This reaction is called Friedel-Crafts-type conversion or known as hydroxyalkylation. Hydroxyalkylations are used in a variety of industrial synthetic methods, including the synthesis of bisphenol resins and Bakelite polymers, in the preparation of malachite green and related colorants, and in the preparation of pharmaceuticals, like bisacodyl and diarylhydantoins. When 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 were reacted with the Brønsted superacid, CF$_3$SO$_2$H (triflic acid), in benzene, the condensation product 207 was obtained in good yield (70%-99%). The mechanism of hydroxyalkylation is thought to involve protonation of an aldehyde and subsequent attack of an arene by the carboxonium ion 204 as described in Scheme 72. 

\[
\text{Ar} = \text{Ph, } 4-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, \text{Me, 3,4-(OCH}_2\text{-CH}_2\text{O)-C}_6\text{H}_3, C}_6\text{H}_5\text{-C}_6\text{H}_4}
\]
Appropriately substituted pyrazoles can also undergo intramolecular Friedel–Crafts-type reactions. For example, the naphthyl-substituted pyrazole 208 gave two products 210 and 211 in roughly equimolar amounts. These products were consistent with a cyclization reaction to form the alcohol 209, which disproportionate to the ketone 211 and methylene-bridged product 210. Even in the presence of benzene, the intramolecular reaction occurred exclusively, and consequently, no hydroxyalkylation product was observed (Scheme 73).

![Scheme 73](image)

Treatment of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 3 with substituted indoles 212 in acetonitrile at room temperature in the presence of phosphotungstic acid, or in chloroform in the presence of Amberlyst 15 resulted in the formation of pyrazolyl bisindoles 213 in 80-90% yields. The synthesized pyrazolyl bisindoles 213 have antimicrobial and antifungal activity (Scheme 74).

![Scheme 74](image)

Ar = Ph, 4-ClC₆H₄, 4-BrC₆H₄, 4-FC₆H₄, 2-thienyl
R¹ = H, Br, NO₂; R² = H, Ph; R³ = H, Et

### 3.5. Miscellaneous reactions
The Baylis-Hillman reaction of substituted pyrazole-3-carbaldehyde 55 and pyrazole-5-carbaldehyde 56 with activated alkene in the presence of DABCO (1,4-
diazabicyclo[2.2.2]octane) as a catalyst, gave allylic alcohols 214-217 in 56-88% yields (Scheme 75).\(^9\)

![Scheme 75](image)

Ar = Ph, 4-MeC₆H₄, 4-ClC₆H₄; EWG = CN, CO₂Me, CO₂Et, CO₂Bu-t, COMe

**Scheme 75**

\(N,N\)-Dimethyl-1-(3-aryl-1-phenyl-1\(H\)-pyrazol-4-yl) methanamine 218 were prepared by reductive amination of the corresponding 3-aryl-1-phenyl-1\(H\)-pyrazole-4-carbaldehydes 3 with DMF and HCO₂H. Quaternization of the tertiary amines 218 using MeI gave the corresponding iodomethylates 219, and alkylation by nonyl chloroacetate gave \(N,N\)-dimethyl-\(N\)-nonyloxycarbonilmethyl-4-pyrazolemethanammonium chloride 220. Pyrazolemethylamines and its ammonium salts exhibit membrane-stabilizing, hemolytic and antibacterial activity against *S. aureus*, *E. coli*, and *C. albicans* (Scheme 76).\(^9\)
Scheme 76

Pyrazolecarboxylic acid chlorides 222 were prepared in 95% yield by treatment of the corresponding aldehydes 221 with Cl₂ over 4 h irradiation using Hg lamp at 20 °C in chlorobenzene in the presence of Na₂CO₃ (Scheme 77).²⁹,³⁰

Scheme 77

Bromination of 1,3-dimethyl- 223a and 1,5-dimethyl-1H-pyrazole-4-carbaldehyde 223b in aqueous alkali afforded 4-bromo-1,3-dimethyl- 224a and 4-bromo-1,5-dimethyl-pyrazoles 224b, respectively (Scheme 78).³¹
Bispyrazole-4-carbaldehyde 225 was reacted with 2-sulfanylethanol in the presence of 10-fold amounts of chloro(trimethyl)silane to give 1,6-bis[3,5-dimethyl-4-(1,4,6-oxadithioctan-5-yl)-1H-pyrazol-1-yl]hexane 226 with high selectivity (Scheme 79).  

Scheme 79

4. Conclusions

This review has attempted to summarize the synthetic methods and reactions of pyrazole-4(3)-carbaldehydes. Many biologically active heterocyclic compounds have been synthesized from that heterocycle. These reactions greatly extended synthetic possibilities in organic chemistry.

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