Pyrazole-carboxaldehydes as versatile precursors for different pyrazole-substituted heterocyclic systems

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Abstract

In the last decade, interest in pyrazole chemistry has grown considerably due to the discovery of fascinating properties demonstrated by a large number of pyrazole derivatives. They occur in a wide range of natural products, dyes, and as scaffolds in a number of drugs and associated pharmaceutical active substances. Substantial attention has been paid to the creation of hybrid molecules in which two heterocycles are bound in a single molecule to enhance their biological effectiveness and overcome drug resistance. In this regard, this review illustrated various methods for the construction of pyrazole-substituted heterocycles and their corresponding fused derivatives using pyrazole carboxaldehydes as effective precursors. The heterocyclic systems mentioned in this review are categorized according to the type of the heterocyclic systems.

Keywords: Vilsmeier-Haack reaction, pyrazole-carboxaldehydes, pyrazole-substituted heterocycles, pyrazole-substituted fused-heterocycles

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References
1. Introduction

Heterocycles are significant classes of compounds that make up more than half of all known organic compounds. They exist in a wide range of medications, most supplements, many natural products, and biomolecules like hormones, antibiotics, alkaloids, vitamins, etc. The vast majority of commercially available synthetic drugs have a heterocyclic structural component. Many heterocyclic compounds were found to exhibit a wide variety of biological activities including antitumor, antibiotics, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antiviral, antidiabetic, herbicide, and fungicide agents. Many of the heterocycles have also many applications such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. Heterocycles are also of great interest as intermediates, protecting groups, chiral auxiliaries, organic catalysts, and metal ligands. In addition, ionic liquids composed of heterocyclic compounds can serve as green solvents as well as catalyst.\(^1\)\textsuperscript{-20}

Nitrogen-containing heterocycles are among the most active compounds due to their large occurrence in natural products. They are among the core structures of various biologically active compounds and are considered as essential roles in many of the chemical reactions occurring in all organisms.\(^19\) They also show numerous applications in chemistry, biology, and other sciences. In addition, nitrogen-containing heterocycles play a significant role in coordination chemistry.\(^21\)

Among different nitrogen-containing heterocycles, pyrazole derivatives represent an interesting class of five-membered heterocycles.\(^11\) Pyrazole is a motif found in a number of molecules that have a wide range of agricultural and pharmaceutical activities.\(^12,22\)

Pyrazole derivatives exhibited a wide variety of biological profiles, such as anti-tuberculosis, anti-AIDS, anti-malarial, anti-microbial, antitumor, antifungal, anti-hyperglycemic agents, anti-depressant agents, anti-convulsant agents, antipyretic agents, and anti-anxiety agents.\(^23\)\textsuperscript{-29}\) The pyrazole ring is involved in diverse therapeutic active compounds. In this respect, a variety of well-known drugs belonging to various categories such as celecoxib, rimonabant, fomepizole, and sildenafil have been recently developed.

Some of the pyrazole derivatives have important applications as brightening agents\(^30\) and some exhibit significant solvatochromic and electroluminescence properties.\(^31\) Their application in material chemistry,\(^32\) semiconductors,\(^33\) liquid crystals,\(^34\) and organic light-emitting diodes\(^35\) have been extensively reported.

The diversity in the numerous potential applications of pyrazoles encouraged the continuous investigation of this class of compounds and prompted authors to search for more effective and selective synthetic routes to this type of compounds and allowing the production of a large number of structurally diverse derivatives with various biological profiles.

Continuing our interest in reviewing various approaches to heterocyclic system synthesis,\(^36\)\textsuperscript{-51}\) this review highlights the different synthetic methods for the preparation of pyrazole-carboxaldehydes and their usefulness as versatile precursors for different pyrazole-substituted heterocyclic systems. Based on the size of the heterocyclic ring as well as the position and number of the heteroatoms, heterocyclic compounds mentioned in this review are arranged.

2. Synthesis of Pyrazole-carboxaldehyde

There have been several important routes to synthesize pyrazole-carboxaldehydes, e.g. (i) Vilsmeier-Haack reaction of hydrazones, (ii) Oxidation of the corresponding alcohols, (iii) Reduction of the corresponding nitrile and (iv) Miscellaneous methods.
2.1. Vilsmeier-Haack reaction

2.1.1 Vilsmeier-Haack reaction of hydrazine. This method is the most common one to synthesize pyrazole-4-carboxaldehydes 2 via the corresponding hydrazonoyl derivatives 1 (Scheme 1, Table 1).

\[
\begin{align*}
&\text{R}^1 \quad \text{R}^2 \\
n &\text{CHO} \\
&\text{N} \quad \text{N} \\
1 &\text{X} = \text{H} \\
2 &
\end{align*}
\]

\( i = N,N\text{-dimethyl formamide (DMF)/ phosphorus oxychloride (POCl}_3)/ \text{heat};^{52-78} 2,4,6\text{-trichloro[1,3,5]triazine (TCT)/DMF/r.t/ Na}_2\text{CO}_3^{,79} \)


Phenylsulfonyl-\(N,N\)dimethylformimidamide-pyrazole-4-carboxaldehydes 4 were obtained by Vilsmeier-Haack reaction of the corresponding benzenesulfonamide hydrazonoyl derivatives 3 with POCl_3 in DMF (Scheme 2).^{80,81}

\[
\begin{align*}
&\text{Ar} = \text{C}_6\text{H}_5, 4\text{-H}_3\text{C}-\text{C}_6\text{H}_4, 4\text{-Br-}\text{C}_6\text{H}_4, 4\text{-Cl-}\text{C}_6\text{H}_4, 4\text{-O}_2\text{N-}\text{C}_6\text{H}_4, 4\text{-H}_3\text{CO-}\text{C}_6\text{H}_4, 4\text{-F-}\text{C}_6\text{H}_4, 2\text{-Thiophene}\n\end{align*}
\]

Scheme 2. Synthesis of phenylsulfonyl-\(N,N\)dimethylformimidamide-pyrazole-4-carboxaldehydes 4.

Table 1. Yields (%) of compounds 2 prepared from hydrazones

<table>
<thead>
<tr>
<th>NO.</th>
<th>R1</th>
<th>R2</th>
<th>Yield%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>H, C6H5, CH3, 4-O2N-C6H4, 4-H3C-C6H4, 3-H3C-C6H4, 2-H3C-C6H4, 4-H3CO-C6H4, 4-Br-C6H4, 4-Cl-C6H4, 4-F-C6H4, 2-HO-C6H4, 3-HO-C6H4, 4-HO-C6H4, 3-O2N-C6H4, 2,4-di-Cl-C6H3, 3,4,5-tri-H3CO-C6H4, tert-Butyl, iso-Butyl, 2-oxo-2H-chromen-3-yl, 6-Y-2-oxo-2H-chromen-3-yl (Y = Cl, Br, O2N), 6,8-Cl2-2-oxo-2H-chromen-3-yl, 8-H3CO-2-oxo-2H-chromen-3-yl, 2-oxo-2H-benzog[\text{g}]{\text{chromen-3-yl}}, 5-Br-thiophen-2-\text{yl}, benzofuran-2-\text{yl}, 3-H3C-benzofuran-2-\text{yl}, 4-HO-6-H3C-2-oxo-2H-pyran-3-\text{yl}, COOEt, 10H-phenothiazin-2-\text{yl}</td>
<td>38-95</td>
<td>52,53,62–66,72–76,54,77–79,55–61</td>
</tr>
<tr>
<td>2</td>
<td>4-O2N-C6H4</td>
<td>C6H5, Benzofuran-2-\text{yl}, 3-H3C-benzofuran-2-\text{yl}, 4-HO-6-H3C-2-oxo-2H-pyran-3-\text{yl}, Benzofuran-2-\text{yl}, 3-</td>
<td>58-94</td>
<td>52,63,75,76</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>NO.</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;, 4-H&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;, 4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;, 4-H&lt;sub&gt;3&lt;/sub&gt;CO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;, 4-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;, 4-F-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;, 4-HO-6-H&lt;sub&gt;3&lt;/sub&gt;C-2-oxo-2H-pyran-3-yl, COOEt</td>
<td>47-92</td>
<td>53,61,66,67,76</td>
</tr>
<tr>
<td>4</td>
<td>4-H&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H, 4-OH-6-H&lt;sub&gt;3&lt;/sub&gt;C-2-oxo-2H-pyran-3-yl, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>42-80</td>
<td>61,76,79</td>
</tr>
</tbody>
</table>

Ramu and Rajagopal<sup>82</sup> reported that the Vilsmeier reaction of the bis-acetyl carbazole hydrazones 5 yielded the corresponding 3,3'-(9-alkyl-carbazole-3,6-diyl)bis(1-phenyl-1H-pyrazole-4-carboxaldehyde) 6 in good yield (Scheme 3).


2.1.2. Vilsmeier-Haack reaction of pyrazole derivatives. 2.1.2.1. Vilsmeier-Haack reaction of pyrazole.

Heating of pyrazole 7 with DMF/POCl<sub>3</sub> gave the corresponding pyrazole-carboxaldehyde 2 (Scheme 4, Table 2).<sup>76,83–85</sup>
Scheme 4. Synthesis of pyrazole-carboxaldehyde 2 from pyrazole 7.

Table 2. Yields (%) of compounds 2 prepared from pyrazoles

<table>
<thead>
<tr>
<th>NO</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Yield%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnO</td>
<td>C₆H₅</td>
<td>H</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>Cl</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>4-HO-6-H₃C-2-oxo-2H-pyran-3-y1</td>
<td>C₆H₅, 4-H₃C-C₆H₄, 4-Cl-C₆H₄, 4-O₂N-C₆H₄, 2,4-(O₂N)₂-C₆H₃</td>
<td>H</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>C₂H₅</td>
<td>H</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>CH₃, C₂H₅, C₃H₇</td>
<td>CH₃</td>
<td>69</td>
<td>85,86</td>
</tr>
</tbody>
</table>

In contrast, 3,5-dimethyl-1H-pyrazole 8 did not undergo formylation at position 4 under analogous conditions. However, the protection of compound 8 through its reaction with methyl acrylate 9 affords methyl-3-(3,5-dimethyl-1H-pyrazol-1-yl)propanoate 10. Subsequent reaction of 10 with POCl₃/DMF afforded methyl 3-(4-formyl-3,5-dimethyl-1H-pyrazol-1-yl)propanoate 11 which undergo alkaline hydrolysis to give methyl 3-(4-formyl-3,5-dimethyl-1H-pyrazol-1-yl)propanoate 12. Subsequent heating of 12 at 250 °C gave 3,5-dimethyl-1H-pyrazole-4-carboxaldehyde 13 (Scheme 5).[^86]

2-(Pyrazol-1-yl)-ethanoles 14 do not undergo Vilsmeier–Haack formylation and instead N-chloroethylpyrazoles 15 were formed. The reaction of N-chloroethylpyrazole 15 with Vilsmeier reagent gave N-chloroethylpyrazole-4-carboxaldehyde 16 in 8-10% yield. On the other hand, synthesis of 1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazole-4-carboxaldehyde 17 took place by acylation of 14 with acetic anhydride or vinyl acetate in the presence of a catalytic amount of copper acetate to give acylated products 17 which readily underwent Vilsmeier-Haack formylation to give 18. Subsequent hydrolysis of 18 afforded 19 which underwent chlorination to give 16 upon treatment of Vilsmeier reagent (Scheme 6).[^87,88]

Scheme 6. Synthesis of 2-(4-formyl-1H-pyrazol-1-yl)ethyl acetate.

Vilsmeier-Haack reaction of bis(3,5-dimethyl-1H-pyrazol-1-yl)methane 19 afforded 1,1'-Methylenebis(3,5-dimethylpyrazole-4-carboxaldehyde) 20 (Scheme 7).

Scheme 7. Synthesis of 1,1'-Methylenebis(3,5-dimethylpyrazole-4-carboxaldehyde) 20.

2.1.2.2. Vilsmeier-Haack reaction of pyrazolone. Wallace and Straley\(^{89}\) reported the synthesis of 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde 22 in good yield by treating the pyrazolinone 21 with DMF and POCl\(_3\) (Scheme 8).


However, it was reported by others, that pyrazol-5-ones 21 underwent formylation using Vilsmeier-Haack conditions to give the corresponding 5-chloropyrazole-4-carboxaldehydes 2 (Scheme 9, Table 3).\(^{90–93}\)

Table 3. Yields (%) of compounds 2 prepared from pyrazolones 21

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>i</th>
<th>Yield%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CH₃, C₆H₅</td>
<td>1)DMF/POCl₃ 2) POCl₃</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅</td>
<td>4-H₃C-C₆H₄, CH₃, C₆H₅, 4-O-C₆H₄, 4-Cl-C₆H₄, 4-H₃CO-C₆H₄</td>
<td>BTC(Bis(trichloromethyl) carbonate) / DMF/ Chlorobenzene, 130 °C</td>
<td>57-86</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>C₆H₅, Pyridyl</td>
<td>DMF/POCl₃ / heat</td>
<td>60-75</td>
<td>92,93</td>
</tr>
</tbody>
</table>

2.1.2.3. Vilsmeier-Haack reaction of aminopyrazoles. Vilsmeier-Haack formylation of 5-aminopyrazoles 23 with excess DMF/POCl₃ under conventional heating⁹⁴ or MW irradiation⁹⁵ led to the formation of 4-formyl-pyrazolyl-dimethylimidoforamidines 24 (Scheme 10, Table 4).⁹⁴,⁹⁵


\[ \text{N-N-Disubstituted-N'}-[1,3-diphenyl-4-formyl-1H-pyrazol-5-yl] \text{formimidamides 25 were synthesized by microwave irradiation of 5-amino-1,3-diphenyl-1H-pyrazole 23 with various amide solvents in the presence of POCl₃ (Scheme 11, Table 5).} \]

Table 4. Yields (%) of compounds 24

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar¹</th>
<th>Ar²</th>
<th>Cond.</th>
<th>Yield%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>4-Cl-C₆H₄, 4-Br- C₆H₄, 4-H₃C-C₆H₄</td>
<td>heat</td>
<td>72-78</td>
<td>⁹⁴</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅, 2-Cl-C₆H₄, 3-H₃C-C₆H₄, 3-Cl-C₆H₄, 3-O₂N-C₆H₄, 4-Br-C₆H₄, 4-H₃CO-C₆H₄</td>
<td>MW</td>
<td>81-94</td>
<td>⁹⁵</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>4-H₃C-C₆H₄, 4-Cl-C₆H₄, 4-H₃CO-C₆H₄, t-Butyl</td>
<td>MW</td>
<td>77-97</td>
<td>⁹⁵</td>
</tr>
</tbody>
</table>
Scheme 11. Synthesis of \(N-N\)-Disubstituted-\(N'\)-[1,3-diphenyl-4-formyl-1H-pyrazol-5-yl]formimidamides 25.

Table 5. Yields (%) of compounds 25

<table>
<thead>
<tr>
<th>Amide solvents</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^1)</td>
<td>(R^2)</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
</tr>
</tbody>
</table>

2.2. Oxidation of the corresponding alcohols

Somnath et al.\(^{96}\) reported that the oxidation of hydroxymethylpyrazole derivatives 26a-c or 27a-c in the presence of pyridinium chlorochromate (PCC) yielded the corresponding pyrazole-carboxaldehydes 28a-c and 29a-c, respectively, in 55-57% and 75-80% yields (Scheme 12).

Scheme 12. Synthesis of pyrazole-carboxaldehydes 28a-c and 29a-c.

The oxidation of hydroxymethyl-(3-pyridyl)pyrazole derivative 30 with PCC afforded (3-pyridyl)pyrazole-4-carboxaldehyde 31 in 41% yield (Scheme 13).\(^{97}\)

Ferrocene-based pyrazole-carboxaldehyde 33 has been formed by oxidation of hydroxymethylpyrazole linked to ferrocene 32 with manganese dioxide (MnO$_2$) in dichloromethane (Scheme 14).\textsuperscript{98}

\[
\begin{align*}
\begin{array}{c}
\text{Ar = C}_6\text{H}_5, \text{Naphthalen}-1-\text{yl}, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{H}_3\text{CO}-\text{C}_6\text{H}_4, 4-\text{tert-Butyl}-\text{C}_6\text{H}_4, 3-F-\text{C}_6\text{H}_4, 4-F-\text{C}_6\text{H}_4, 2-\text{Cl-}\text{C}_6\text{H}_4, 3-\text{Cl-}\text{C}_6\text{H}_4, 3-\text{Cl-2-F-}\text{C}_6\text{H}_3, \text{CH}_3.
\end{array}
\end{align*}
\]

\textbf{Scheme 14.} Synthesis of ferrocene-based pyrazole-carboxaldehyde 33.

1,3-Diaryl-1H-pyrazole-4-carboxaldehydes 2 were prepared in good to excellent yields via the oxidation of the corresponding (1,3-diaryl-1H-pyrazol-4-yl)methanol 34 by iron(III) chloride hexahydrate FeCl$_3.6$H$_2$O catalyzed by a free radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 15).\textsuperscript{99}

\[
\begin{align*}
\begin{array}{c}
\text{R = H, Br, Cl, OEt}
\end{array}
\end{align*}
\]

\textbf{Scheme 15.} Synthesis of 1,3-diaryl-1H-pyrazole-4-carboxaldehydes 2 from alcohol 34.

\textbf{2.3. Reduction of the corresponding pyrazolecarbonitrile}

The reduction of 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(methylsulfinyl)-1H-pyrazole-3-carbonitrile 35 in the presence of di-iso-butylaluminium hydride (iso-Bu)$_2$AlH afforded the corresponding pyrazole-4-carboxaldehyde 2 (Scheme 16).\textsuperscript{100}

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

\textbf{Scheme 16.} Synthesis of pyrazole-4-carboxaldehyde 2 by reduction of pyrazolecarbonitrile 35.
2.4. Hydrolysis of (pyrazolyl)methanimine

Hydrolysis of N-aryl-1-(3-(trimethylsilyl)-1H-pyrazol-4-yl)methanimine 36 gave 3-(trimethylsilyl)-1H-pyrazole-4-carboxaldehyde 37 (Scheme 17).\(^\text{101}\)

![Scheme 17. Synthesis of 3-(trimethylsilyl)-1H-pyrazole-4-carboxaldehyde 37.](image)

2.5. Miscellaneous methods

Arbačiauskienė et al.\(^\text{83}\) reported that the treatment of 3-(benzyloxy)-4-bromo-1-phenyl-1H-pyrazole 38 with n-BuLi gave rise to selective bromine-lithium exchange. Subsequent quenching of the intermediate 4-lithiopyrazole with DMF afforded pyrazole-carboxaldehyde 2 (Scheme 18).

![Scheme 18. Synthesis of pyrazole-carboxaldehyde 2.](image)

3. Synthesis of Pyrazole-substituted Heterocycles

3.1. Pyrazole-substituted monoheterocyclic ring

3.1.1. Monocyclic five-membered with one heteroatom. 3.1.1.1. Furan derivatives. Fekri et al.\(^\text{102}\) reported that the one-pot multi-component reaction of 4-pyrazole-carboxaldehyde 2, ethyl pyruvate 39, and bromine gave 2,3-dihydrofuranediones 40 under ultrasonic irradiation (Scheme 19).

![Scheme 19. Synthesis of 2,3-dihydrofuranediones 40.](image)

R\(^1\) = H, Cl; R\(^2\) = H, NO\(_2\); R\(^3\) = OCH\(_3\), OH, H, Cl.

3.1.1.2. Pyrrole derivatives. Ragab et al.\(^\text{67}\) reported that the Claisene-Schmidt condensation between pyrazole-carboxaldehydes 2 and 4-chloracetophenone 41 afforded the corresponding chalcones 42 which upon reaction with 4-substituted-benzaldehyde 43 in DMF in the presence of potassium cyanide as a catalyst afforded 1,4-
diketones 44. Compounds 44 were cyclized using ammonium acetate in acetic acid under Paal-Knorr reaction conditions to yield the corresponding pyrrole derivatives 45 (Scheme 20).

Scheme 20. Synthesis of pyrrole derivatives 45.

3.1.2. Monocyclic five-membered with two heteroatoms. 3.1.2.1. Pyrazole derivatives. 3.1.2.1.1. Synthesis of pyrazole derivatives from chalcone carrying pyrazole. Under different reaction conditions, a series of chalcones 42 were synthesized through the Claisen–Schmidt condensation of pyrazole-4-carboxaldehyde 2 with aryl(hetero)methylene ketones 41. The chalcone derivatives 42 were then reacted with hydrazine derivatives 46 to give the corresponding 4,5-dihydro-1H-pyrazole 47. On the other hand, the reaction of chalcones 42 with hydrazine hydrate in the presence of acid gave the acylated 4,5-dihydro-1H-pyrazole 48 (Scheme 21).

On the other hand, the same reaction of chalcones 42 with hydrazine hydrate or phenylhydrazine in the presence of acetic acid gave the corresponding 1H-pyrazoles 49 and 50 respectively. The reaction of chalcones 42 with iodine in dimethyl sulfoxide (DMSO) followed by reaction with hydrazine hydrate afforded pyrazoles 51 (Scheme 22).

\[
\text{ArCHO} + \text{RNHNH}_2 \xrightarrow{i} \text{ArN}_2\text{H}_2 \xrightarrow{ii} \text{ArN}_2\text{H}_2 \xrightarrow{iii} \text{ArN}_2\text{H}_2
\]
NaOH,\textsuperscript{59,104,114,115} ii) two drops AcOH/ stirring r.t.,\textsuperscript{111,116} MeOH/ HCl/ reflux,\textsuperscript{113} AcOH/ reflux,\textsuperscript{103} H\textsubscript{2}SO\textsubscript{4}/ AcOH/ reflux\textsuperscript{26,112} or grinding,\textsuperscript{112} EtOH/ NaOH/reflux,\textsuperscript{57,59,104,114} EtOH,\textsuperscript{59,104,112} grinding\textsuperscript{112} or dioxan.\textsuperscript{105}

**Scheme 21.** Synthesis of 4,5-dihydro-1H-pyrazole 47 and 4,5-dihydro-1H-pyrazole 48.

\[
\begin{align*}
\text{Ar}^1 &= \text{C}_6\text{H}_5; \quad \text{Ar}^2 = \text{C}_6\text{H}_5, \text{Naphthalen}-2-\text{yl}; \quad \text{Ar}^3 = 5-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 5-\text{Cl}-2-\text{HO}-\text{C}_6\text{H}_3, 4-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 3-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 5-\text{H}_3\text{C}_2-2-\text{HO}-\text{C}_6\text{H}_3, 5-\text{Br}-2-\text{HO}-\text{C}_6\text{H}_3, 5-\text{F}-2-\text{HO}-\text{C}_6\text{H}_3, 3,5-\text{di}-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 3,5-\text{di}-\text{Cl}-2-\text{HO}-\text{C}_6\text{H}_3, 4,6-\text{di}-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 5-\text{Cl}-3-\text{H}_3\text{C}-2-\text{HO}-\text{C}_6\text{H}_3, 10\text{H}-\text{Phenothiazin}-2-\text{yl}; \quad i) \text{EtOH/ KOH/ reflux,} \quad \text{ii) (1)I}_2/ \text{DMSO}
\end{align*}
\]

**Scheme 22.** Synthesis of 1H-pyrazoles 49, 50 and 51.

Ali\textsuperscript{117} reported the synthesis of 1-((dimethylphosphoryl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-5-phenyl-1H-pyrazole 52 by reaction of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one 42 with \(p,p\)-dimethylphosphinic hydrazide 46 in the presence of acetic acid (Scheme 23).

**Scheme 23.** Synthesis of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-5-phenyl-1H-pyrazole 52.

**3.1.2.1.2. Synthesis of pyrazole derivatives from arylidene malononitrile carrying pyrazole.** Ismail et al.\textsuperscript{118} reported the synthesis of 2-((1-(3-chlorophenyl))-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene)malononitrile 54 by heating of pyrazole-4-carboxaldehyde 2 and malononitrile 53. Heating of 54 at reflux with hydrazine hydrate 46 in ethanol/ piperidine gave 4-((1-(3-chlorophenyl))-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene)-4H-pyrazole-3,5-diamine 55 (Scheme 24).
Scheme 24. Synthesis of 4-((1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene)-4H-pyrazole-3,5-diamine 55.

On the other hand, the reaction of 2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile 54 with p,p'-dimethylphosphinic hydrazide afforded 5-amino-1-(dimethylphosphoryl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-pyrazole-4-carbonitrile 56\(^\text{117}\) (Scheme 25).

Scheme 25. Synthesis of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-pyrazole-4-carbonitrile 56.

3.1.2.1.3. Synthesis of pyrazole derivatives from cyanoacetohydrazide carrying pyrazole. Atta-Allah et al.\(^\text{119}\) reported that treatment of the pyrazole-4-carboxaldehyde 2 with cyanoacetohydrazide 57 in dioxane at reflux gave 2-cyano-N'-[1,3-diphenyl-1H-pyrazol-4-yl)methylene]acetohydrazide 58. Heating N-condensation product 58 in ethanol in the presence of a catalytic amount of piperidine, gave a mixture of pyrazolone and hydroxyl pyrazole derivatives 59 in a ratio of 2:3 (Scheme 26).


3.1.2.1.4. Synthesis of pyrazole derivatives from cyanoacrylohydrazide carrying pyrazole. Fahmy et al.\(^\text{120}\) reported that heating of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde 2 with cyanoacetoxydrazide 57 in ethanol containing a few drops of acetic acid gave pyrazolinone derivative 60. Stirring of pyrazole-carboxaldehyde 2 and cyanoacetoxydrazide 57 in ethanol containing few drops of triethylamine
gave 3-[1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl]-2-cyanoacrylohydrazide 61. Heating of 61 at reflux in acetic acid afforded compounds 60 (Scheme 27).

\[ \text{Scheme 27. Synthesis of pyrazolinone derivatives 60.} \]

3.1.2.1.5. **Miscellaneous methods.** Youssef et al.\textsuperscript{121} reported that heating of quinazolinone derivative 61 with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 in ethanol at reflux followed by heating with hydrazine hydrate at reflux gave 5-(1,3-diphenyl-1H-pyrazol-4-yl)-3H-pyrazol-3-one 63 and 3-amino-2-methylquinazolin-4(3H)-one 62 as a by-product (Scheme 28).

Muthineni et al.\textsuperscript{122} reported that the four-component reaction of hydrazine hydrate 46, ethylacetate derivative 64, pyrazole-carboxaldehyde 2, and 3,5-dimethyl isoxazole 65 afforded the corresponding 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-arylethyl)-1H-pyrazol-3-oles 66 (Scheme 29).

\[ \text{Scheme 28. Synthesis of 3-amino-2-methylquinazolin-4(3H)-one 62 and 5-(1,3-diphenyl-1H-pyrazol-4-yl)-3H-pyrazol-3-one 63.} \]

\[ \text{Scheme 29. Synthesis of 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-arylethyl)-1H-pyrazol-3-oles 66.} \]
3.1.2.2. Imidazole derivatives. Abou Elmagd et al.\textsuperscript{123} reported that heating of \(N\)-(1-(1,3-diphenyl-1H-pyrazol-4-yl)-3-oxo-3-(2-((phenyl-2-azaneyl)carbonothioyl) hydrazineyl) prop-1-en-2-yl)benzamide \textsuperscript{67} with o-phenylenediamine \textsuperscript{68} in ethanol at reflux produced a mixture of 3-amino-5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-2-phenyl-3,5-dihydro-4H-imidazol-4-one \textsuperscript{69} and 1,3-dihydro-2H-benzo[d]imidazole-2-thione \textsuperscript{70} (Scheme 30).

![Scheme 30. Synthesis of 3,5-dihydro-4H-imidazol-4-one 69 and 2H-benzo[d]imidazole-2-thione 70.](image)

Aly et al.\textsuperscript{125} reported that heating of 3-aryl-1-phenyl-1H-pyrazole-4-carboxaldehydes \textsuperscript{2} with benzamidine hydrochloride \textsuperscript{71} and ethyl chloroacetate \textsuperscript{64} gave dihydroimidazolone derivatives \textsuperscript{72} (Scheme 31).

Heating of pyrazole-4-carboxaldehyde \textsuperscript{2} with the appropriate isothiocyanate \textsuperscript{73} and glycine \textsuperscript{74} in glacial acetic acid at reflux afforded thioxoimidazolidin-4-ones \textsuperscript{75} \textsuperscript{118,126} (Scheme 32).

![Scheme 31. Synthesis of dihydroimidazolone derivatives 72.](image)

Shirole et al.\textsuperscript{127} reported that imidazoles \textsuperscript{79} were synthesized by a multi-component reaction of benzil \textsuperscript{76}, aniline derivatives \textsuperscript{77}, 1-phenyl-3-p-tolyl-1H-pyrazole-4-carboxaldehyde \textsuperscript{2} and ammonium acetate \textsuperscript{78} in the presence of 1-butyl-3-methyl-1-imidazolium tetrafluoroborate [BMIM][BF\textsubscript{4}] as a catalyst (Scheme 33).

![Scheme 32. Synthesis of thioxoimidazolidin-4-ones 75.](image)
R = CH₃, H, F, Cl, Br, NO₂; R¹ = H, Cl; i = Conventional Method: Reflux 14-15 h / [BMIM] [BF₄]/Ethanol (68-78%); Green Method: MW at 240 W/ [BMIM][BF₄]/Solvent Free 10-12 min (84-89%).

Scheme 33. Synthesis of imidazoles 79.

Banothu et al.⁸¹ reported that 1,3-diphenyl-4-(4,5-diphenyl-1H-imidazol-2-yl)-1H-pyrazoles 81 were synthesized by the condensation of benzoin 80 with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 and ammonium acetate 78 using Brønsted acidic ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl) phosphonium hydrogen sulfate [(4-SB)T(4-SPh)PHSO₄] as a catalyst (Scheme 34).

Scheme 34. Synthesis of 1,3-diphenyl-4-(4,5-diphenyl-1H-imidazol-2-yl)-1H-pyrazoles 81.

Under different reaction conditions, a series of imidazolylpyrazoles 82 was synthesized by the multicomponent reaction of pyrazole-4-carboxaldehydes 2, benzil 76, and ammonium acetate 78⁸¹-⁸⁵ (Scheme 35).

Reaction conditions; a: NH₄OAc / Acetic acid / Reflux (69-95%),⁸⁹-⁹¹ b: NH₄OAc / Acetic acid / MW (84-91%),⁸⁹ c: NH₄OAc / Glutamic acid / ethanol / Reflux (85-94%),⁹⁰ d: NH₄OAc / 120 °C using Brønsted acidic ionic liquid, [(4-SB)T(4-SPh)PHSO₄] (98%),⁹¹ e: NH₄OAc/ Reflux 4-4.5hhrs/ [BMIM] [BF₄]/ Ethanol (68-72%),⁹² f: NH₄OAc/ Ultra-sonication (80-90 min)[BMIM][BF₄]/ Ethanol (78-80%),⁹² g: NH₄OAc/ MW irradiation 240 watt (7-9 min) [BMIM][BF₄]/ Solvent Free (80-86%);⁹² R¹ = C₆H₅, 4-O₂N-C₆H₄; R² = C₆H₅, 4-Cl-C₆H₄, 4-F-C₆H₄, 4-Br-C₆H₄, 4-O₂N-C₆H₄, 4-H₂CO-C₆H₄, 4-H₂C-C₆H₄, 3-O₂N-C₆H₄, 4-(H₅C₆)-C₆H₄, 3,4-diCl-C₆H₃, 3,4-diF-C₆H₃, 2-Thienyl, 2-Fluorobenzyl, CH₃, Coumarinyl, 6-Br-coumarinyl; R³ = H, CH₃.

Scheme 35. Synthesis of imidazolylpyrazoles 82.
3.1.2.3. Oxazole derivatives. Bekhit and Fahmy\textsuperscript{133} reported the synthesis of oxazolidine-3-carboxylate 84 \textit{via} reaction of 3-[(5-bromo-2-thienyl)-1-phenyl-1H-pyrazole-4-carboxaldehyde 2 with L-serine 83, followed by N-protection using di-\textit{tert}-butyl dicarbonate (Boc)\textsubscript{2}O (Scheme 36).

![Scheme 36. Synthesis of oxazolidine-3-carboxylate 84.](image)

Aly \textit{et al.}\textsuperscript{125} reported that heating of 3-aryl-1-phenyl-1H-pyrazole-4-carboxaldehydes 2 with glycine derivatives 74 and sodium acetate in acetic anhydride afforded the corresponding 4-(3-aryl-1-phenyl-1H-pyrazole-4-ylmethylene)-2-substituted oxazol-5-(4H)-ones 85 (Scheme 37).

![Scheme 37. Synthesis of 2-substituted oxazol-5-(4H)-ones 85.](image)

3.1.2.4. Isoxazole derivatives. Madhavilatha \textit{et al.}\textsuperscript{134} reported that pyrazole-carboxaldehydes 2 was converted to 4-hydroxypyrazoles 86 upon treatment with \textit{meta}-chloroperoxybenzoic acid (mCPBA). Next, 4-hydroxypyrazoles 86 reacted with propargyl bromide 87 in tetrahydrofuran (THF)/DMF using NaH as a base to give O-propargylated pyrazole derivative 88. The reaction of 88 with aryl aldoximes 89 afforded isoxazole functionalized pyrazole derivatives 90 (Scheme 38).

![Scheme 38. Synthesis of isoxazole functionalized pyrazole derivatives 90.](image)
Reaction of α,β-unsaturated ketones 42 with an aqueous solution of hydroxylamine hydrochloride 91, and sodium acetate in ethanol at reflux gave isoxazole derivatives 9259,104,114,135 (Scheme 39).

\[
\text{ArCHO} + \text{NH}_2\text{OH, HCl} \rightarrow \text{Ar}^{1}\text{N}=\text{OAr}^{2}
\]

\(\text{Ar}^{1} = \text{C}_6\text{H}_5, \text{4-H}_2\text{N-C}_6\text{H}_4, \text{4-Cl-C}_6\text{H}_4, \text{4-Br-C}_6\text{H}_4, \text{4-F-C}_6\text{H}_4, \text{2-HO-C}_6\text{H}_4, \text{4-HO-C}_6\text{H}_4, \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{4-H}_3\text{C-C}_6\text{H}_4, \text{3-O}_2\text{N}-\text{C}_6\text{H}_4, \text{4-O}_2\text{N-C}_6\text{H}_4, \text{Thiophen-2-yl}, 10\text{H}-\text{Phenothiazin-2-yl} ; \text{Ar}^{2} = \text{C}_6\text{H}_5, \text{3-Cl-C}_6\text{H}_4; \text{Ar}^{3} = \text{C}_6\text{H}_5, \text{2-H}_3\text{CO-C}_6\text{H}_4, \text{4-}
\text{H}_3\text{CO-C}_6\text{H}_4
\]


3.1.2.5. Thiazole derivatives. Heating a solution of pyrazole-carboxaldehyde 2 with L-cysteine (\(R^3 = \text{H}\)) or L-penicillamine (\(R^3 = \text{CH}_3\)) 83 followed by \(N\)-protection using (Boc)\(_2\)O provided thiazolidine-4-carboxylic acid 93.\(^{133,136}\) Condensation of pyrazole-4-carboxaldehyde 2 with arylamine 77 gave Schiff’s bases 94 which reacted with thioglycolic acid 95 to give the thiazolidinedione derivatives 99\(^{136,137}\) (Method A). Taherkhorsand et al.\(^{138}\) and Nikpassand et al.\(^{139}\) reported also the synthesis of 2-pyrazole-3-phenyl-1,3-thiazolidine-4-ones 96 via a multi-component reaction of pyrazole-carboxaldehydes 2, arylamine 77, thioglycolic acid 95 in the presence of DSDABCOC\(^{138}\) or OImDSA\(^{139}\) (Method B) (Scheme 40).

DSDABCOC: ionic liquid 1,4-disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride
OImDSA: 2-oxoimidazolidine-1,3-disulfonic acid

\[
\text{R}^1 = \text{C}_6\text{H}_5, \text{5-Bromothiophen-2-yl} ; \text{R}^2 = \text{C}_6\text{H}_5, \text{4-H}_3\text{C-C}_6\text{H}_4, \text{4-Cl-C}_6\text{H}_4, \text{3-O}_2\text{N-C}_6\text{H}_4, \text{4-HO-C}_6\text{H}_4; \text{R}^3 = \text{H, CH}_3; \text{Ar}^{1} = \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{2-H}_3\text{C-4-O}_2\text{N-C}_6\text{H}_4, \text{C}_6\text{H}_5, \text{4-O}_2\text{N-C}_6\text{H}_4, \text{4-H}_3\text{C-C}_6\text{H}_4, \text{4-Fluorobenzyl, 4-(4-Chlorophenyl)thiazol-2-yl.}
\]

Scheme 40. Synthesis of 2-pyrazole-3-phenyl-1,3-thiazolidine-4-ones 96.

Visagaperumal et al.\(^{70}\) reported that thiazolidin-4-ones 96 has been synthesized by stirring of pyrazole-4-carboxaldehyde 2 with 2-mercaptoacetic acid 95 and different substituted aromatic amines 77 in dry toluene under the effect of microwave heating for 12 min (Scheme 41).
\[
\text{ArCHO} + \text{HSCH}_2\text{COOH} + \text{RNH}_2 \rightarrow \text{R}_\text{N-S-}\text{O}\text{Ar} \quad \text{Toluene} \quad \text{12 min} \quad \text{MW} \quad \text{R} = \text{C}_6\text{H}_5, 4-\text{O}_2\text{N-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{C}_7\text{H}_7\text{O}, 4-\text{C}_7\text{H}_7\text{O}, 4-\text{C}_7\text{H}_3\text{O}, 3-\text{O}_2\text{N-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4.
\]

**Scheme 41.** Synthesis of thiazolidin-4-ones 96.

One-pot multi-component cyclocondensation of pyrazole-4-carboxaldehydes 2, thiosemicarbazide 97, and maleic anhydride 98 using baker’s yeast as a catalyst afforded pyrazol-4-yl substituted thiazoles 99.\(^{140}\) Thiazoles 99 were also synthesized via two-steps-reactions. Thus, cyclocondensation reaction of pyrazole-4-carboxaldehydes 2 with substituted thiosemicarbazide derivatives 97 afforded the corresponding thiosemicarbazone derivatives 100\(^{62,103,126,141–147}\) which underwent cyclization with maleic anhydride 98 to furnish thiazole derivatives 99\(^{144,146}\) (Scheme 42).

\[
\begin{align*}
\text{Ar} & = \begin{cases} \text{R}_1^1 = \text{C}_6\text{H}_5, 3-\text{Cl-C}_6\text{H}_4; \\ \text{R}_2^2 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, 4-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{O}_2\text{N-C}_6\text{H}_4; \\ \text{R}_3^3 = \text{H}, \text{C}_6\text{H}_5, 4-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, \text{Cyclohexane.} 
\end{cases}
\end{align*}
\]

Scheme 42. Synthesis of thiazole derivatives 99.

Nikpassand et al.\(^{148}\) reported that stirring a mixture of a pyrazole-carboxaldehyde 2, thiosemicarbazide 97, bromoacetophenone 101 in the presence of [PDBMDIm]Br as a catalyst at room temperature afforded 2-hydrazonyl-4-phenylthiazoles 102 (Scheme 43).

Cyclization of thiosemicarbazone derivatives 100 either by ethyl chloroacetate,\(^{141}\) methyl α-bromopropionate,\(^{141}\) ethyl bromoacetate,\(^{62,142,143}\) chloroacetic acid,\(^{149}\) diethyl-2-bromomalonate\(^{146}\) or methyl bromoacetate\(^{126,64}\) furnished the thiazole derivatives 103 (Scheme 44).

Similarly, Some 4-arylthiazol-2-yl-hydrazines derivatives 104\(^{62,126,141–144,146,147}\) were prepared by reaction of the appropriate α-haloketones 101 with the corresponding thiosemicarbazone 100. The reaction of thiosemicarbazone derivatives 100 with the appropriate hydrazonoyl halides 105 gave 5-phenylazo-thiazol-2-yl-
Compounds 106 were alternatively obtained by reaction of ω-bromoacetophenone 101 with 100 to give 1-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-2-(4-phenylthiazol-2-yl)hydrazine 107 followed by reaction with benzenediazonium chloride 108 (Scheme 45).

![Chemical Reaction Diagram](image)

**Scheme 43.** Synthesis of 2-hydrayzonyl-4-phenylthiazoles 102.

**Scheme 44.** Synthesis of thiazole derivatives 103.

**Scheme 45.** Synthesis of thiazol-2-yl-hydrazines derivatives 104 and 106.
On the other hand, treatment of pyrazolyl hydrazone derivative 100 with thioglycolic acid 95 acid gave the corresponding thiazolidinedione derivative 109\(^{145}\) (Scheme 46).

**Scheme 46.** Synthesis of thiazolidinedione derivatives 109.

Treatment of thiosemicarbazone derivatives 100 with ethyl bromoacetate\(^{142}\) or diethyl-2-bromomalonate\(^{146}\) 64 in the presence of sodium acetate led to the corresponding thiazolidinediones 110\(^{142,146}\) (Scheme 47).

Gaffer *et al.*\(^{150}\) reported that condensation of pyrazolin-5-one derivative 111 with Pyrazole-carboxaldehyde 2 in acetic acid and fused sodium acetate yielded the corresponding condensation product 112 which underwent further heterocyclization reaction with bromoacetone and phenacyl bromide 101 to give the corresponding thiazolyl-pyrazole derivatives 113 (Scheme 48).

**Scheme 47.** Synthesis of thiazolidinediones 110.

**Scheme 48.** Synthesis of thiazolyl-pyrazole derivatives 113.

Treatment of pyrazole-carboxaldehyde 2 with malonic acid hydrazide 114 afforded pyrazolyl malonohydrazone derivative 115 which reacted with p-chlorobenzaldehyde 43 to give the corresponding benzylidene derivative 116. The reaction of 116 with thioglycolic acid 95 gave the dithiazolidinone derivative 117\(^{145}\) (Scheme 49).
Bhatt and Sharma\textsuperscript{130} reported the synthesis of tri-substituted thiazoles derivatives \textbf{119} by the reaction of benzil \textbf{76} with pyrazole-4-carboxaldehydes \textbf{2} and ammonium thiocyanate \textbf{118} (Scheme 50).

Bekhit \textit{et al.}\textsuperscript{136} reported that 3-aryl-1-phenyl-1H-pyrazole-4-aldoximes \textbf{121} were obtained by the condensation of 3-aryl-1-phenyl-1H-pyrazole-4-carboxaldehydes \textbf{2} with hydroxylamine hydrochloride \textbf{120} in ethanol containing anhydrous sodium acetate. Dehydration of the oximes \textbf{121} with acetic anhydride (Ac\textsubscript{2}O) afforded the cyano derivatives \textbf{122}. Cyclization of the cyano derivatives \textbf{122} with cysteamine hydrochloride \textbf{123} in the presence of sodium hydroxide afforded thiazolidine derivatives \textbf{124} (Scheme 51).

\textbf{3.1.2.6. 1,2-Oxaphosphole derivatives.} Ali\textsuperscript{117} reported that heating of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one \textbf{42}\textsuperscript{116} with diethylphosphite \textbf{125} in boron trifluoride etherate (BF\textsubscript{3}.Et\textsubscript{2}O) afforded 4-(2-ethoxy-2-oxido-5-phenyl-2,3-dihydro-1,2-oxaphosphol-3-yl)-1,3-diphenyl-1H-pyrazole \textbf{126} (Scheme 52).
Scheme 52. Synthesis of 1,3-diphenyl-1H-pyrazole 126.

3.1.3. Monocyclic five-membered with three heteroatoms. 3.1.3.1. 1,3,4-Thiadiazole derivatives. Heating of thiosemicarbazone derivatives 100 in acetic anhydride at reflux gave the corresponding 3-acetyl-2,3-dihydro-1,3,4-thiadiazole derivatives 127\(^{62,142,143}\) or corresponding 1,3,4-thiadiazole derivatives 128\(^{126}\) (Scheme 53).

![Scheme 52](image)

R\(^1\) = C\(_6\)H\(_5\), 4-(H\(_2\)NO\(_2\)S)-C\(_6\)H\(_4\); R\(^2\) = 4-Cl-C\(_6\)H\(_4\), 4-Br-C\(_6\)H\(_4\), 4-H\(_3\)CO-C\(_6\)H\(_4\), C\(_6\)H\(_5\), 4-(H\(_5\)C\(_6\)H\(_2\)CO)-C\(_6\)H\(_4\); R\(^3\) = H, C\(_6\)H\(_5\), 4-Cl-C\(_6\)H\(_4\).

Scheme 53. Synthesis of 1,3,4-thiadiazole derivatives 128.

Oxidative cyclization of the thiosemicarbazones 100 afforded the corresponding 1,3,4-thiaoxadiazoles 128\(^{151,143}\) (Scheme 54).

![Scheme 53](image)

R\(^1\) = C\(_6\)H\(_5\), 2-H\(_3\)CO-C\(_6\)H\(_4\), 2-H\(_3\)C-C\(_6\)H\(_4\), 4-Cl-C\(_6\)H\(_4\), 2,4-di(O\(_2\)N)-C\(_6\)H\(_3\), 4-(H\(_2\)NO\(_2\)S)-C\(_6\)H\(_4\); R\(^2\) = C\(_6\)H\(_5\), 7-HO-4-H\(_3\)C-2-oxo-2H-chromen-8-yl; R\(^3\) = H, C\(_6\)H\(_5\), 4-Cl-C\(_6\)H\(_4\); i = Br\(_2\)/CH\(_3\)COOH,\(^{151}\) FeCl\(_3\)/ (Dioxane/ethanol)/ Reflux.\(^{143}\)

Scheme 54. Synthesis of 1,3,4-thiaoxadiazoles 128.

Abou Elmagd et al.\(^{123}\) reported that heating of thiosemicarbazide 67\(^{124}\) with phosphoryl trichloride at reflux afforded 1,3,4-thiadiazole derivatives 129 (Scheme 55).
Scheme 55. Synthesis of 1,3,4-thiadiazole derivatives 129.

Treatment of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 with the appropriate methyl(benzyl)carbodithioate 130 in 2-propanol gave the corresponding alkyl carbodithioates 131. The reaction of the appropriate hydrazonoyl halides 105 with alkyl carbodithioates 131 in ethanol containing triethylamine (TEA) afforded 2,3-dihydro-1,3,4-thiadiazoles 132. Compounds 132 were alternatively obtained by the reaction of ethyl 2-hydrazono-3-phenyl-1,3,4-thidiazoline-5-carboxylate 133 with pyrazole-carboxaldehyde 2103 (Scheme 56).

Scheme 56. Synthesis of 2,3-dihydro-1,3,4-thiadiazoles 132.

3.1.3.2. 1,2,3-Triazole derivatives. Dayakar et al.152 reported that reduction of pyrazole-carboxaldehydes 2 using sodium borohydride (NaBH₄) provided the corresponding alcohols 134 which was converted to the corresponding azides 135 in the presence of diphenyl phosphoramid azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Reaction of azides 135 with propargyl alcohol 87, phenyl acetylenes 137 and dimethyl/ diethyl acetylene dicarboxylate 139 in the presence of copper(II) sulfate pentahydrate (CuSO₄·5H₂O)/ sodium ascorbate in aqueous alcohol medium provided the corresponding pyrazolyl-1H-1,2,3-triazolyl alcohols 136, pyrazolyl-1H-1,2,3-triazoles 138 and pyrazolyl-1H-1,2,3-triazolyl carboxylates 140, respectively (Scheme 57).
Scheme 57. Synthesis of pyrazolyl-1H-1,2,3-triazoles 136, 138 and 140.

The reaction of aryl azides 141 with O-propargylated pyrazole derivatives 88 afforded the corresponding 1,4-disubstituted-1,2,3-triazole-linked pyrazole hybrids 142 (Scheme 58).

Scheme 58. Synthesis of 1,4-disubstituted-1,2,3-triazole-linked pyrazole hybrids 142.

3.1.3.3 1,2,4-Triazole derivatives. Heating of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde 2 with semicarbazide hydrochloride or thiosemicarbazide 97 in absolute ethanol at reflux in the presence of few drops of glacial acetic acid afforded 1,2,4-triazole-3(4H)-one 143. On the other hand, heating of pyrazole-carboxaldehyde 2 with thiosemicarbazide 97 in water as a green solvent afforded the 5-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1,2,4-triazolidine-3-thiones 144 (Scheme 59).
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**Scheme 59.** Synthesis of 5-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1,2,4-triazolidine-3-thiones 144.

3.1.3.4. 1,3,4-Oxadiazole derivatives. Renuka et al.\(^{151}\) reported that the oxidative cyclization of semicarbazones 100 using bromine as an oxidant in acetic acid at room temperature yielded the corresponding 1,3,4-oxadiazoles 145 (Scheme 60).

**Scheme 60.** Synthesis of 1,3,4-oxadiazoles 145.

Farghaly et al.\(^{62}\) reported the synthesis of aroylhydrazones 153 by heating the pyrazole-carboxaldehyde 2 with acid hydrazide 152 in ethanol. Cyclization of aroylhydrazones 153 upon treatment with acetic anhydride gave the corresponding oxadiazoline derivatives 154 (Scheme 61).

**Scheme 61.** Synthesis of oxadiazoline derivatives 154.

Abu-Zaied et al.\(^{65}\) reported that 5-(3-isobutyl-1-phenyl-1H-pyrazole-4-yl)-1,3,4-oxadiazole-2-thiol 150 was prepared by the reaction of ethanolic potassium hydroxide solution of 3-isobutyl-1-phenyl-1H-pyrazole-4-carboxyhydrazide 149 with carbon disulfide (CS\(_2\)) (Scheme 62).
Scheme 62. Synthesis of 5-(3-isobutyl-1-phenyl-1H-pyrazole-4-yl)-1,3,4-oxadiazole-2-thiol 150.

Abou Elmagd et al.\textsuperscript{123} reported that heating of thiosemicarbazide derivative 67 in glacial acetic acid at reflux afforded the oxazolone derivative 151 (Scheme 63).

Scheme 63. Synthesis of oxazolone derivative 151.

3.1.4. Monocyclic six-membered with one heteroatom. 3.1.4.1. Pyran derivatives. Heating of 2-((1,3-diphenylpyrazol-4-yl)methylene)malononitrile 54 with ethyl acetoacetate 64 in methylene chloride at reflux in the presence of triethylamine gave the ethyl 6-amino-5-cyano-4-(1,3-diphenylpyrazol-4-yl)-2-methyl-4H-pyran-3-carboxylate derivative 152\textsuperscript{141} (Scheme 64).

Scheme 64. Synthesis of ethyl 6-amino-5-cyano-4-(1,3-diphenylpyrazol-4-yl)-2-methyl-4H-pyran 152.

3.1.4.2. Pyridine derivatives. 3.1.4.2.1. Synthesis of pyridine derivatives from chalcone carrying pyrazole. Hawass et al.\textsuperscript{153} reported that the potassium salt of unsaturated carbonyl compounds 42 reacted with 1,4-dibromobutane to afford bis-unsaturated carbonyl compound 153. Cyclocondensation of compound 153 with 2-cyanoethanethioamide 154 in pyridine at reflux gave bis(pyridine-2(1H)-thione) derivative 155 (Scheme 65).
Scheme 65. Synthesis of bis(pyridine-2(1H)-thione) derivative 155.

The reaction of α,β-unsaturated ketones 42 with malononitrile 53 in ethanol at reflux in the presence of ammonium acetate afforded the corresponding 2-amino-3-cyano-pyridine derivatives 156. On the other hand, a reaction of 42 with 53 in the presence of either sodium methoxide/ methanol or sodium ethoxide/ethanol gave the corresponding 2-alkoxynicotinonitriles 157 (Scheme 66).


Heterocyclization of chalcones carrying pyrazole 42 with ethyl cyanoacetate 64 and ammonium acetate gave the corresponding 2-oxo-1,2-dihydropyridine-3-carbonitrile 158. On the other hand, heating chalcones 3 with cynothioacetamide 154 in ethanol at reflux afforded the corresponding 3-cyano-pyridine-2(1H)-thiones 159. Moreover, reaction of chalcones 42 with 2-cyanoacetohydrazide 57 afforded 1-amino-2-oxo-1,2-dihydropyridine-3-carbonitrile 160 (Scheme 67).
Scheme 67. Synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile 158 and 3-cyano-pyridine-2(1H)-thiones 159.

Heating of \(\alpha,\beta\)-unsaturated ketones 42 with different phenacyl pyridium bromides 101 in acetic acid at reflux in the presence of ammonium acetate under Kröhnke’s conditions gave the pyridinyl pyrazoles 161\(^{158-160}\) (Scheme 68).

\[
\text{Ar} = \begin{array}{c}
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

\[
\text{42} \quad \text{NH}_4\text{OAc} \quad \text{AcOH} \quad \text{Ar} = \begin{array}{c}
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

\[
\text{101} \quad \text{AcOH} \quad \text{Ar} = \begin{array}{c}
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

\[
\text{161} \quad 52-83\%
\]

\( R^1 = 2,4\text{-di-F-C}_6\text{H}_4, \text{C}_6\text{H}_5; R^2 = 4\text{-Br-C}_6\text{H}_4, \text{C}_6\text{H}_5, 4\text{-H}_3\text{CO-C}_6\text{H}_4, 4\text{-H}_3\text{C-C}_6\text{H}_4; Ar^1 = \text{C}_6\text{H}_5, 4\text{-Br-C}_6\text{H}_4, 4\text{-H}_3\text{C-C}_6\text{H}_4, 4\text{-F-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 4\text{-H}_3\text{CO-C}_6\text{H}_4, 2\text{-oxo-2H-chromen-3-yl}, 8\text{-H}_3\text{C}-2\text{-oxo-2H-chromen-3-yl}; Ar^2 = \text{C}_6\text{H}_5, 4\text{-Cl-C}_6\text{H}_4, 4\text{-Methyl-2-oxo-3-phenyl-2H-chromen-6-yl}, 8\text{-H}_3\text{C}-2\text{-oxo-2H-chromen-3-yl}, 8\text{-Br-2-oxo-2H-chromen-3-yl}, 2\text{-oxo-2H-chromen-3-yl}, 8\text{-H}_3\text{C}-2\text{-oxo-2H-chromen-3-yl}, 3\text{-oxo-3H-benzo[f]chromen-2-yl.}
\]

Scheme 68. Synthesis of pyridinyl pyrazoles 161.

3.1.4.2.2. Synthesis of pyridine derivatives from aryliden malononitrile carrying pyrazole. The reaction of pyrazol-4-ylmethylene-malononitrile 54 and 2-cyanoacetamide or 2-cyanothioacetamide 154 in sodium ethoxide at reflux afforded 4,6-diamino-5-\((\text{1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)}\)methylene)-2,5-dihydro-2-oxothio)pyridine-3-carbonitriles 162\(^{118}\). Reaction of pyrazol-4-ylmethylene-malononitrile 54 with malononitrile dimer, ethyl cyanoacetate dimer or ethyl-3-amino-2,4-dicyanobut-2-enoate 163 gave the corresponding dihydropyridine derivatives 164\(^{161,162}\). On the other hand, reaction of 54 with 2-cyanoacetohydrazide 57 in ethanol in the presence of piperidine gave 1,6-diamino-4-\((1,3\text{-diphenyl-1H-pyrazol-4-yl)}\)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile 165\(^{119}\) (Scheme 69).
\[ R^1 = 3\text{-}\text{Cl-C}_6\text{H}_4, C_6\text{H}_5; R^2 = 4\text{-}H_3\text{CO-C}_6\text{H}_4, C_6\text{H}_5, 4\text{-}H_3\text{C-C}_6\text{H}_4; M = H, Cl; X = S, O; Y = CN, CO_2Et; Z = CN, CO_2Et. \]

**Scheme 69.** Synthesis of dihydropyridine derivatives 162 and 164.

Condensation of pyrazol-4-ylmethylenmalononitrile 54 with different aryl ketones 41 in the presence of sodium methoxide/ethoxide gave the corresponding 2-alkyloxy-pyridine-3-carbonitriles 166.\(^{163}\) On the other hand, pyrazol-4-ylmethylenmalononitrile 54\(^{125,164}\) could be cyclized with acetone and ammonium acetate to give the corresponding 3-amino-6-methylpyridine-2-carbonitriles 167\(^{125}\) (Scheme 70).

\[ R^1 = 3\text{-}\text{Cl-C}_6\text{H}_4; R^2 = \text{Pyren-1-yl}; Ar^1 = C_6\text{H}_5, 2\text{-}\text{Thienyl}, 2\text{-}\text{Pyridinyl}, 2\text{-}\text{Furanyl}, 2\text{-}\text{Pyrryl}; R^3 = \text{CH}_3, C_2\text{H}_5. \]

**Scheme 70.** Synthesis of pyridine-2/3-carbonitriles 166 and 167.

**3.1.4.2.3. Synthesis of pyridine derivatives from ethyl arylidencyanoacetate linked to pyrazole moiety.** The Knoevenagel condensation reaction of pyrazole-4-carboxaldehyde 2 with ethyl cyanoacetate 64 gave ethyl-2-cyano-2-acrylate derivative 168 which was then reacted with acetophenone 41 to afford 2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile 169\(^{165}\) (Scheme 71).

\[ R^1 = C_6\text{H}_5; R^2 = 2\text{-}\text{HO-3,4-di-H}_3\text{CO-C}_6\text{H}_2. \]

**Scheme 71.** Synthesis of 2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile 169.
3.1.4.2.4. Synthesis of pyridine derivatives from hydrazone carrying pyrazole. Treatment of hydrazone derivative 58 with ethyl-2-cyano-3-arylacrylate 170 yielded pyridinone 171. On the other hand, the reaction of 58 with 2-arylidene malononitrile derivatives 172 afforded 6-amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles 173 (Scheme 72).

![Scheme 72. Synthesis of pyridinones 171 and 173.](image)

3.1.4.2.5. Synthesis of pyridine derivatives from reaction of pyrazole-carboxaldehyde with 3-aminocrotononitrile. The pseudo-multicomponent reaction of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 with two equivalent of 3-aminocrotononitrile 174 in glacial acetic acid afforded 3,5-dicyano-2,6-dimethyl-1,4-dihydropyridines 175. On the other hand, the one-pot multicomponent reaction of pyrazole-4-carboxaldehyde 2, 3-aminocrotononitrile 174 and ethyl acetoacetate (EAA) or/ and ethyl acetoacetate (MAA) 64 in the presence of Fe3+ montmorillonite clay K-10 or HY-zeolite under microwave irradiation in aqueous medium afforded the corresponding 1,4-dihydropyridine derivatives 176 (Scheme 73).

![Scheme 73. Synthesis of 1,4-dihydropyridine derivatives 175 and 176.](image)
3.1.4.2.6. Synthesis of pyridine derivatives via one-pot reaction of pyrazole-carboxaldehyde. One-pot reaction of pyrazole-4-carboxaldehyde 2 with an appropriate aromatic ketone 41 and malononitrile 53 in the presence of ammonium acetate 78 furnished 2-amino-nicotinonitrile 177\textsuperscript{120,155,171,172} (Scheme 74).

\[
\text{ArCHO} + \text{Ar}^1\text{COCH}_3 + \text{CH}_2(\text{CN})_2 + \text{NH}_4\text{OAc} \xrightarrow{i} \text{Ar}^1\text{NNNH}_2 \quad \text{177}
\]

\(R^1 = \text{C}_6\text{H}_5, 3-\text{Cl-C}_6\text{H}_4; R^2 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{H}_3\text{C-C}_6\text{H}_4; \text{Pyren}-1\text{-yl, 4-Cl-C}_6\text{H}_4, 4-\text{O}_2\text{N-C}_6\text{H}_4, 2-\text{HO-C}_6\text{H}_4, 2-\text{CH}_3\text{O-C}_6\text{H}_4, 3-\text{O}_2\text{N-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4 4-\text{OH-C}_6\text{H}_4; \text{Ar}^1 = \text{C}_6\text{H}_5, 4-\text{Cl-C}_6\text{H}_4, 4-\text{HO-C}_6\text{H}_4, 4-\text{H}_3\text{C-C}_6\text{H}_4, 2-\text{Thienyl}, 2-\text{F-C}_6\text{H}_4, 2-\text{H}_3\text{CO-C}_6\text{H}_4, 2-\text{Br-C}_6\text{H}_4, 2-\text{O}_2\text{N-C}_6\text{H}_4, 4-\text{HO}-2\text{-oxo}-2\text{H}-\text{chromen}-3\text{-yl}, 4-\text{HO}-8\text{-H}_3\text{C}-2\text{-oxo}-2\text{H}-\text{chromen}-3\text{-yl}, (4\text{-H}_3\text{C}-2\text{-oxo}-2\text{H}-\text{chromen}-7\text{-yl})\text{oxy, Benzofuran}-2\text{-yl}. i = \text{Ethanol/ reflux,120,155} (\text{Fe}^\text{+3 K-10 clay or HY-zeolite})\text{MW irradiation,171 Ac}_2\text{O,172 butanol/ reflux.155}
\]

Scheme 74. Synthesis of 2-amino-nicotinonitriles 177.

On the other hand, the reaction of equimolecular amounts of 1,3-diphenyl-1\text{-H}-pyrazole-4-carboxaldehyde 2, appropriate aromatic ketone 41 and malononitrile 53 in the presence of aniline afforded the corresponding pyridine-3-carbonitriles 178\textsuperscript{155} (Scheme 75).

\[
\text{ArCHO} + \text{R}^3\text{COCH}_3 + \text{CH}_2(\text{CN})_2 \xrightarrow{\text{PhNH}_2} \text{Ar}^1\text{NNNH}_2 \quad \text{178}
\]

\(R^1 = \text{C}_6\text{H}_5; R^2 = \text{C}_6\text{H}_5; R^3 = \text{C}_6\text{H}_5, 2\text{-Thienyl}; R^4 = \text{C}_6\text{H}_5, 4\text{-H}_3\text{C-C}_6\text{H}_4, 2\text{-Thienyl.}
\]

Scheme 75. Synthesis of pyridine-3-carbonitriles 178.

Heating pyrazole-4-carboxaldehyde 2 with aromatic ketone 41 and ethyl cyanoacetate 64 in the presence of ammonium acetate afforded 2-oxo-1,2-dihydropyridine-3-carbonitrile 179\textsuperscript{120,155,173} Moreover, a mixture of pyrazole-4-carboxaldehyde 2 with aromatic ketone 41 and ethyl cyanoacetate 72 in the presence of aniline afforded the corresponding 2-oxo-1,2-dihydropyridine-oxo-1-phenyl-3-carbonitrile 180\textsuperscript{155} (Scheme 76).

\[
\text{ArCHO} + \text{Ar}^1\text{COCH}_3 \xrightarrow{\text{AcONH}_4} \text{Ar}^1\text{NNNH}_2 \quad \text{180}
\]

\(R^1 = \text{C}_6\text{H}_5, 3-\text{Cl-C}_6\text{H}_4; R^2 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{CO-C}_6\text{H}_4, \text{Pyren}-1\text{-yl; Ar}^1 = \text{C}_6\text{H}_5, 4-\text{Cl-C}_6\text{H}_4, 4-\text{HO-C}_6\text{H}_4, 4-\text{H}_3\text{C-C}_6\text{H}_4, 2-\text{Thienyl}, 2-\text{F-C}_6\text{H}_4, 2-\text{H}_3\text{CO-C}_6\text{H}_4, 2-\text{Br-C}_6\text{H}_4, 2-\text{O}_2\text{N-C}_6\text{H}_4.
\]

Scheme 76. Synthesis of 1,2-dihydropyridine-3-carbonitriles 179 and 180.
One-pot condensation of substituted pyrazol-4-carboxaldehydes 2, two equivalents of acetophenones 41 and ammonium acetate in the presence of solid sodium hydroxide and using polyethylene glycol (PEG-400) as a green solvent\(^\text{174}\) or acetic acid\(^\text{175}\) afforded the corresponding 2,4,6-triaryl substituted pyridines (Krohnke pyridines) 181\(^\text{174,175}\) (Scheme 77).

\[
\text{ArCHO} + \text{Ar}^1 \text{CH}_3 \xrightarrow{i} \text{NH}_4\text{OAc} \to \text{Ar}\text{N} \text{Ar}^1 \xrightarrow{i = \text{PEG-400/ NaOH(s), AcOH}} \text{Ar} = \begin{array}{c}
\text{181} \\
\text{70-85%}
\end{array}
\]

\(R^1 = \text{C}_6\text{H}_5; \text{R}^2 = 4-\text{Cl-C}_6\text{H}_4, 4-\text{HO-C}_6\text{H}_4, \text{C}_6\text{H}_5; \text{Ar}^1 = 5-\text{Cl}-2-\text{HO-C}_6\text{H}_3, 3-\text{Br}-5-\text{Cl}-2-\text{HO-C}_6\text{H}_2, 3-\text{I}-5-\text{Cl}-2-\text{HO-C}_6\text{H}_2, 3-\text{I}-5-\text{H}_3\text{C}-2-\text{HO-C}_6\text{H}_2, 3-\text{I}-4-\text{H}_3\text{C}-2-\text{HO-C}_6\text{H}_2, 2-\text{Mercapto}-4-\text{methyl-1-phenyl-1H-imidazol-5-yl}.
\]

Scheme 77. Synthesis of 2,4,6-triaryl-substituted pyridines.

Under various conditions, the Hantzsch condensation reaction of pyrazole-4-carboxaldehyde 2 with \(\text{β}-\text{ketoester 64}\) and ammonium acetate or ammonia afforded the corresponding dihydropyridines 182.\(^\text{131,176-183}\) Similarly, \(N\)-aryl-1,4-dihydropyridines 183 were prepared by heating the 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2, ethyl acetoacetate/acetylacetone 64 and substituted anilines\(^\text{184}\) in methanol at reflux (Scheme 78).

\[
\text{R}^1 = \text{C}_6\text{H}_5, \text{H}; \text{R}^2 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{C-C}_6\text{H}_4, 4-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4, 4-\text{O}_2\text{N-C}_6\text{H}_4, 3-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{H}_3\text{CO}_2\text{S-C}_6\text{H}_4, 2-\text{O}_2\text{N-C}_6\text{H}_4, 4-\text{H}_3\text{CS-C}_6\text{H}_4, 3-\text{O}_2\text{N-4-Cl-C}_6\text{H}_3, \text{Pyrazin-2-yl}, 4-\text{HO-C}_6\text{H}_4, 3,4-\text{di-Cl-C}_6\text{H}_3, 3,4-\text{di-F-C}_6\text{H}_3; \text{R}^3 = \text{OC}_2\text{H}_5, \text{OCH}_3, \text{CH}_3; \text{R}^4 = \text{CH}_3, \text{C}_2\text{H}_5; \text{Ar}^1 = \text{C}_6\text{H}_5, 2-\text{H}_3\text{C-C}_6\text{H}_4, 3-\text{H}_3\text{C-C}_6\text{H}_4, 4-\text{H}_3\text{C-C}_6\text{H}_4, 2-\text{Cl-C}_6\text{H}_4, 3-\text{Cl-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 2-\text{H}_3\text{CO-C}_6\text{H}_4, 3-\text{H}_3\text{CO-C}_6\text{H}_4, 4-\text{H}_3\text{CO-C}_6\text{H}_4; i = \text{NH}_4\text{OAc/ EtOH/ reflux, 176 NH}_4\text{OAc/ 20 mol% SA/ EtOH/ reflux, 177 NH}_4\text{OAc/ MgO nanotube/ Acetonitrile, reflux, 178 NH}_3\text{dropwise/ CH}_3\text{OH/ reflux, 179 NH}_3\text{OAc/ heat 80 °C/ silica 10 mol%, 180 NH}_4\text{OAc/ w. b/ EtOH, 131 NH}_4\text{OAc/ Bismuth tungstate (Bi}_2\text{WO}_6 5 mol%, 181 NH}_4\text{OAc/ Gu.HCl/ 25-30°C, 182 NH}_4\text{OAc/ Acetonitrile, reflux, 40 °C, 300 W, 30 °C}. 183
\]

Scheme 78. Synthesis of 1,4-dihydropyridines 182 and 183.

3.1.5. Monocyclic six-membered with two heteroatoms. 3.1.5.1. Pyrimidine derivatives. Condensation of pyrazol-4-ylmethylene malononitrile 54 with thiourea 184 in the presence of sodium ethoxide solution at reflux gave the corresponding pyrimidine derivatives 195.\(^\text{165}\) Also, it was reported that the cyclocondensation of pyrazole-carboxaldehyde 2 with urea\(^\text{120}\) or thiourea 184\(^\text{120,185}\) and ethyl cyanoacetate 64 in the presence of
sodium ethoxide\textsuperscript{120} or potassium carbonate\textsuperscript{385} gave the corresponding 2-oxo(thioxo)pyrimidine derivatives \textbf{185} (Scheme 79).

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) [draw] {\textbf{Ar}};
  \node (b) at (1,0) [draw] {\textbf{CN}};
  \node (c) at (2,0) [draw] {\textbf{CN}};
  \node (d) at (0,-1) [draw] {\textbf{NH}_2\text{CSNH}_2};
  \node (e) at (1,-1) [draw] {\textbf{NaOEt}};
  \node (f) at (2,-1) [draw] {\textbf{ArCHO}};
  \node (g) at (0,-2) [draw] {\textbf{Ar}};
  \node (h) at (1,-2) [draw] {\textbf{X}};
  \node (i) at (2,-2) [draw] {\textbf{CNCH}_2\text{COOC}_2\text{H}_5};
  \node (j) at (0,-3) [draw] {\textbf{R}^1};
  \node (k) at (1,-3) [draw] {\textbf{R}^2};

  \path (a) edge node [above] {73\%} (b);
  \path (b) edge node [above] {75-79\%} (c);
  \path (a) edge node [above] {\textbf{R}^1=C_6\text{H}_5, 3-Cl-C_6\text{H}_4}; (d);
  \path (b) edge node [above] {\textbf{R}^2= 2-HO-3,4-di-H_3CO-C_6\text{H}_4, 4-H_3CO-C_6\text{H}_4, C_6\text{H}_5}; (e);
  \path (c) edge node [above] {\textbf{X}= O, S} (f);

  \path (g) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (h);
  \path (h) edge node [above] {\textbf{NaOEt}} (i);
  \path (i) edge node [above] {186, 104, 109, 114, 115, 187, 141, 157} (k);
  \path (j) edge node [above] {188} (m);

  \path (m) edge node [above] {\textbf{Ar}} (n);
  \path (n) edge node [above] {\textbf{Ar}} (o);
  \path (n) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (p);
  \path (p) edge node [above] {\textbf{NaOEt}} (q);
  \path (q) edge node [above] {184, 104, 114, 115} (r);
  \path (r) edge node [above] {189} (s);

  \path (o) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (t);
  \path (t) edge node [above] {\textbf{NaOEt}} (u);
  \path (u) edge node [above] {184} (v);
  \path (v) edge node [above] {186} (w);

  \path (w) edge node [above] {58-81\%} (x);
  \path (x) edge node [above] {187} (y);

  \path (y) edge node [above] {83\%} (z);

\end{tikzpicture}
\end{center}

\textbf{Scheme 79.} Synthesis of 2-oxo(thioxo)pyrimidine derivatives \textbf{185}.

The reaction of \(\alpha,\beta\)-unsaturated ketone \textbf{42} with thiourea \textbf{184} in the presence of sodium ethoxide solution at reflux was reported to give either the corresponding pyrimidine derivatives \textbf{186, 104, 114, 115, 187, 141, 157} or \textbf{188}\textsuperscript{186} (Scheme 80).

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) [draw] {\textbf{Ar}};
  \node (b) at (1,0) [draw] {\textbf{CN}};
  \node (c) at (2,0) [draw] {\textbf{CN}};
  \node (d) at (0,-1) [draw] {\textbf{NH}_2\text{CSNH}_2};
  \node (e) at (1,-1) [draw] {\textbf{NaOEt}};
  \node (f) at (2,-1) [draw] {\textbf{ArCHO}};
  \node (g) at (0,-2) [draw] {\textbf{Ar}};
  \node (h) at (1,-2) [draw] {\textbf{X}};
  \node (i) at (2,-2) [draw] {\textbf{CNCH}_2\text{COOC}_2\text{H}_5};
  \node (j) at (0,-3) [draw] {\textbf{R}^1};
  \node (k) at (1,-3) [draw] {\textbf{R}^2};

  \path (a) edge node [above] {73\%} (b);
  \path (b) edge node [above] {75-79\%} (c);
  \path (a) edge node [above] {\textbf{R}^1=C_6\text{H}_5, 3-Cl-C_6\text{H}_4}; (d);
  \path (b) edge node [above] {\textbf{R}^2= 2-HO-3,4-di-H_3CO-C_6\text{H}_4, 4-H_3CO-C_6\text{H}_4, C_6\text{H}_5}; (e);
  \path (c) edge node [above] {\textbf{X}= O, S} (f);

  \path (g) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (h);
  \path (h) edge node [above] {\textbf{NaOEt}} (i);
  \path (i) edge node [above] {186, 104, 114, 115, 187, 141, 157} (k);
  \path (j) edge node [above] {188} (m);

  \path (m) edge node [above] {\textbf{Ar}} (n);
  \path (n) edge node [above] {\textbf{Ar}} (o);
  \path (n) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (p);
  \path (p) edge node [above] {\textbf{NaOEt}} (q);
  \path (q) edge node [above] {184} (r);
  \path (r) edge node [above] {186, 104, 114, 115} (s);

  \path (o) edge node [above] {\textbf{NH}_2\text{CSNH}_2} (t);
  \path (t) edge node [above] {\textbf{NaOEt}} (u);
  \path (u) edge node [above] {184} (v);
  \path (v) edge node [above] {186} (w);

  \path (w) edge node [above] {58-81\%} (x);
  \path (x) edge node [above] {187} (y);

  \path (y) edge node [above] {83\%} (z);

\end{tikzpicture}
\end{center}

\textbf{Scheme 80.} Synthesis of pyrimidinethione derivatives \textbf{186, 187} and \textbf{188}.

On the other hand treatment of chalcones \textbf{42} with guanidine hydrochloride or guanidine sulfate \textbf{184} at reflux afforded pyrimidin-2-amines \textbf{189}\textsuperscript{104, 109, 114, 115} (Scheme 81).

Ismail \textit{et al.}\textsuperscript{118} reported that the reaction of pyrazol-4-ylmethylene malononitrile \textbf{54} with urea or thiourea \textbf{184} afforded 4,6-diamino-5-benzylidenepyrimidin-2(5H)-ones/(thiones) \textbf{190} (Scheme 82).
\[ \text{NH}_2\text{C}(\text{NH})\text{NH}_2 \cdot X \rightarrow \text{NH}_2\text{C}(\text{NH})\text{NH}_2 \cdot \text{H}_2\text{SO}_4, \text{HCl} \]

\[ \text{NaOH or KOH, ETOH, reflux} \]

\[ \text{X} = \text{H}_2\text{SO}_4, \text{HCl} \]

R\textsuperscript{1} = C\textsubscript{6}H\textsubscript{5}, 3-Cl-C\textsubscript{6}H\textsubscript{4}; R\textsuperscript{2} = C\textsubscript{6}H\textsubscript{5}, 4-F-C\textsubscript{6}H\textsubscript{4}, 4-Cl-C\textsubscript{6}H\textsubscript{4}, 3-Br-C\textsubscript{6}H\textsubscript{4}, 4-Br-C\textsubscript{6}H\textsubscript{4}, 3-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}, 4-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}, 4-H\textsubscript{3}C-C\textsubscript{6}H\textsubscript{4}, 4-H\textsubscript{3}CO-C\textsubscript{6}H\textsubscript{4}; Ar\textsuperscript{1} = \text{Pyridin}-3-yl, \text{Thiophen}-2-yl, C\textsubscript{6}H\textsubscript{5}, 4-H\textsubscript{3}CO-C\textsubscript{6}H\textsubscript{4}, 4-H\textsubscript{3}C-C\textsubscript{6}H\textsubscript{4}, 4-Cl-C\textsubscript{6}H\textsubscript{4}, 4-F-C\textsubscript{6}H\textsubscript{4}, 4-HO-C\textsubscript{6}H\textsubscript{4}, 2-HO-C\textsubscript{6}H\textsubscript{4}, 4-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}, 4-Br-C\textsubscript{6}H\textsubscript{4}.

\textbf{Scheme 81.} Synthesis of pyrimidin-2-amines 189.

\[ \text{NH}_2\text{C}X\text{NH}_2 \rightarrow \text{NH}_2\text{C}X\text{NH}_2 \cdot \text{H}_2\text{SO}_4, \text{HCl} \]

\[ \text{EtOH, EtONa} \]

R\textsuperscript{1} = 3-Cl-C\textsubscript{6}H\textsubscript{4}; R\textsuperscript{2} = 4-H\textsubscript{3}CO-C\textsubscript{6}H\textsubscript{4}; X = O, S

\textbf{Scheme 82.} Synthesis of 4,6-diamino-5-benzylidenepyrimidin-2(5H)-ones/(thiones) 190.

Knovenagel condensation of pyrazole-carboxaldehyde 2 with barbituric acid, thiobarbituric acid 191 afforded the corresponding pyrimidine-2,4,6(1H,3H,5H)-trione and dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione 192\textsuperscript{118,126} (Scheme 83).

\[ \text{NH}_2\text{C}X\text{NH}_2 \rightarrow \text{NH}_2\text{C}X\text{NH}_2 \cdot \text{H}_2\text{SO}_4, \text{HCl} \]

\[ \text{EtOH, pip} \]

R\textsuperscript{1} = 3-Cl-C\textsubscript{6}H\textsubscript{4}, C\textsubscript{6}H\textsubscript{5}; R\textsuperscript{2} = 4-H\textsubscript{3}CO-C\textsubscript{6}H\textsubscript{4}, 4-(H\textsubscript{5}C\textsubscript{6}H\textsubscript{2}CO)-C\textsubscript{6}H\textsubscript{4}; X = O, S

\textbf{Scheme 83.} Synthesis of dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione 192.

Under various conditions multi-component reaction of pyrazole-4-carboxaldehyde 2 with ethylacetoacetate,\textsuperscript{120,131,187–189} methylacetoacetate,\textsuperscript{131,187} acetylacetone\textsuperscript{120,131} or butanamides\textsuperscript{64,190,191} 64 and urea,\textsuperscript{64,120,131,187,189–191} thiourea,\textsuperscript{64,103,120,187,188,191} guanidine\textsuperscript{187} or 1-methylurea\textsuperscript{189} 184 afforded the corresponding 2-oxo (thioxo) pyrazole substituted pyrimidine derivatives 193 (Scheme 84).

TEAA = triethylammonium acetate; p-TsOH = p-toluenesulfonic acid
R\(^1\) = C\(_6\)H\(_5\), 3-Cl-C\(_6\)H\(_4\), 4-F-C\(_6\)H\(_4\), 2,4-di-F-C\(_6\)H\(_3\); R\(^2\) = 3,4-di-Cl-C\(_6\)H\(_3\), 4-di-F-C\(_6\)H\(_3\), 4-H\(_3\)CO-C\(_6\)H\(_4\), 4-F-C\(_6\)H\(_4\), 4-Cl-C\(_6\)H\(_4\),
4-Br-C\(_6\)H\(_4\), 4-O\(_2\)N-C\(_6\)H\(_4\), 4-H\(_3\)C-C\(_6\)H\(_4\), C\(_6\)H\(_5\), 2,4-di-Cl-5-F-C\(_6\)H\(_2\), 3-Br-C\(_6\)H\(_4\), 3-O\(_2\)N-C\(_6\)H\(_4\), CH\(_3\), C\(_2\)H\(_5\), 4-HO-C\(_6\)H\(_4\), 2-HO-
C\(_6\)H\(_4\); R\(^3\) = O\(_2\)H\(_5\), OCH\(_3\), CH\(_3\), Pyridin-2-yl-NH, (5-H\(_5\)C-pyridin-2-yl)-NH, (5-Br-pyridin-2-yl)-NH, C\(_6\)H\(_5\)NH, NH-(4-H\(_3\)C-
C\(_6\)H\(_4\)), NH-(4-Cl-C\(_6\)H\(_4\)), NH-(2-Cl-C\(_6\)H\(_4\)), NH-(4-O\(_2\)N-C\(_6\)H\(_4\)), NH-(2-F-C\(_6\)H\(_4\)), NH-(3-F-C\(_6\)H\(_4\)), NH-
(3-Cl-C\(_6\)H\(_4\)), NH-(2-O\(_2\)N-C\(_6\)H\(_4\)), NH-(2-F-C\(_6\)H\(_4\)), NH-(3-O\(_2\)N-C\(_6\)H\(_4\)); R\(^4\) = H, CH\(_3\); X = S, O, NH. i = HCl/ 
EtOH,\(^{103,120,131,187,188}\) TEA,\(^{190}\) p-TsOH 40 mol %/ EtOH,\(^{64}\) CH\(_3\)OH/ HCl,\(^{191}\) FeCl\(_3\).6H\(_2\)O,\(^{192}\) Phosphotungstic acid.\(^{189}\)

Scheme 84. Synthesis of 2-oxo (thioxo) pyrazole substituted pyrimidine derivatives 193.

On the other hand condensation of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-
carboxaldehyde 2 with ethyl cyanoacetate or ethyl acetoacetate 64 in the presence of guanidine hydrochloride 184 gave 2-amino-5-cyano/acetyl-6-hydroxy-4-aryl pyrimidines 194\(^{104}\) (Scheme 85).

\[
\begin{align*}
\text{2} & \quad + \quad \text{64} \quad \xrightarrow{i} \quad \text{194} \\
\end{align*}
\]

R\(^1\) = 3-Cl-C\(_6\)H\(_4\); R\(^2\) = 4-H\(_3\)CO-C\(_6\)H\(_4\); R = CN, CH\(_3\)CO

Scheme 85. Synthesis of 2-amino-5-cyano/acetyl-6-hydroxy-4-aryl pyrimidines 194.

3.1.6. Monocyclic six-membered with three heteroatoms. 3.1.6.1. Triazine derivatives. Heating a solution of thiocarbamide derivative 67 in acetic acid and HCl at reflux produced 5-((1,3-diphenyl-1H-pyrazole-4-
yl)methyl)-3-(phenylamino)-1,2,4-triazin-6(1H)-one 195\(^{123}\) (Scheme 86).

\[
\begin{align*}
\text{67} & \quad \xrightarrow{\text{HCl/ AcOH}} \quad \text{68} \\
\end{align*}
\]

Scheme 86. Synthesis of 5-((1H-pyrazole-4-yl)methyl)-3-(phenylamino)-1,2,4-triazin-6(1H)-one 195.

3.1.7. Monocyclic six-membered with four heteroatoms. 3.1.7.1. Tetrazine derivatives. El-Bordany et al.\(^{145}\) reported that the reaction of pyrazolyl thiocarbohydrazone derivative 100 with 4-chlorobenzaldehyde 43 in
ethanol at reflux gave instead of a condensation product, the cyclized adduct pyrazolyl-tetrazinethione derivative 196. Reaction of 100 with hydrazine hydrate 46 in ethanol at reflux afforded corresponding 1,2,4,5-tetrazine derivative 197. Compound 197 was alternatively obtained by reaction of 196 with hydrazine hydrate 46 in ethanol at reflux (Scheme 87).

Scheme 87. Synthesis of pyrazolyl-tetrazinethione derivatives 196 and 197.

3.1.7.2. Oxadiazaphosphinin derivatives. Ali 117 reported that heating of 2-cyano-N-[1,3-diphenyl-1H-pyrazol-4-ylmethylidene]acetohydrazide 58 with diethyl phosphite 125 and boron trifluoride etherate afforded [2-ethoxy-2-oxido-3-(1,3-diphenyl-1H-pyrazol-4-yl)-2H-1,4,5,2-oxadiazaphosphinin-6-yl]acetonitrile 198 in good yield (Scheme 88).

Scheme 88. Synthesis of [3-(1H-pyrazol-4-yl)-2H-1,4,5,2-oxadiazaphosphinin-6-yl]acetonitrile 198.

3.2. Pyrazole-substituted fused heterocyclic system
3.2.1. Pyrazole-substituted bicyclic systems. 3.2.1.1. Fused [5-6] system with two heteroatoms. 3.2.1.1.1. Thiazolo[3,2-a]pyridine derivative. El-Emary et al. 166 reported that condensation of 2-cyanomethyl-4-thiazolinone 199 with 1,3-diphenyl-pyrazole-4-carboxaldehyde 2 yielded 2-(5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile 200. Heating of 200 with malononitrile in ethanol at reflux gave the corresponding thiazolo[3,2-a]pyridine derivative 201. On the other hand, treatment of compound 201 with arylidenemalononitriles 172 gave the thiazolo[3,2-a]pyridine derivatives 202. Thiazolo[3,2-a]pyridines 202 were also synthesized via a multi-component reaction of compound 200 with aromatic aldehyde 43 and malononitrile 53 in ethanol containing piperidine at reflux (Scheme 89).

Abdel Hafiz et al.\textsuperscript{162} reported that the formation of 5-amino-3-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-α]pyridine-6-carbonitrile 203 was performed by the reaction of pyrazol-4-ylmethylene malononitrile 54 with thiazol-4(5H)-one derivatives 199 (Scheme 90).

\[ \text{Scheme 90. Synthesis of 5-amino-3-oxo-tetrahydro-5H-thiazolo[3,2-α]pyridine-6-carbonitrile 203.} \]

3.2.1.1.2. Fused [5-6] system with three heteroatoms. 3.2.1.1.2.1. Pyrazolo[3,4-b]pyridine derivatives. Jachak et al.\textsuperscript{193} reported that pyrazolo[3,4-b]pyridine derivatives 205 were synthesized by one-pot cyclocondensation of 5-amino-3-aryl-1H-phenylpyrazoles 204, p-substituted benzyloacetonitriles 101, and pyrazole-4-carboxaldehydes 2 using ammonium acetate or triethylamine as a catalyst (Scheme 91).

\[ \text{Scheme 91. Synthesis of pyrazolo[3,4-b]pyridine derivatives 205.} \]

3.2.1.1.2.2. Thiazolo[3,2-α]pyrimidine derivatives. Sahu et al.\textsuperscript{194} reported the synthesis of a series thiazolo[3,2-α]pyrimidine-6-carboxylate derivatives 207 through a multi-component reaction of ethyl acetoacetate 64,
pyrazole-4-carboxaldehydes 2, and an excess amount of substituted aminothiazole 206 using ammonium metavanadate (NH$_4$VO$_3$) as a catalyst (Scheme 92).

![Scheme 92. Synthesis of thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives 207.](image)

3.2.1.1.2. 1H-Imidazo[4,5-b]pyridine derivatives. Kumbar et al.\textsuperscript{195} reported the synthesis of 6-bromo-1H-imidazo[4,5-b]pyridines 209 by condensation of 6-bromo-pyridine-2,3-diamine 208 with pyrazole-4-carboxaldehydes 2 in ethanol at reflux or under microwave irradiation (Scheme 93).

![Scheme 93. Synthesis of 6-bromo-1H-imidazo[4,5-b]pyridines 209.](image)

3.2.1.1.3. Fused [5-6] system with four heteroatoms. 3.2.1.1.3.1. [1,2,4]Triazolo[4,3-a]pyrimidine derivatives. Kamal et al.\textsuperscript{196} reported that hydrazone derivatives 211 were obtained by heating the 2-hydrzino-4,6-dimethylpyrimidine 210 with the appropriate pyrazole-4-carboxaldehyde derivatives 2 in ethanol at reflux. [1,2,4]Triazolo[4,3-a]-pyrimidines 212 were obtained by oxidation of hydrazone derivatives 211 using iodobenzebediacetate (IBD) in dichloromethane (DCM) at room temperature (Scheme 94).

![Scheme 94. Synthesis of [1,2,4]triazolo[4,3-a]-pyrimidines 212.](image)
3.2.1.3.2. Triazolo[1,5-a]pyrimidine derivatives. Shejale et al.\textsuperscript{157} and El-Emary and Bakhite\textsuperscript{141} reported that the reaction of chalcones 42 with 3-amino-s-triazole 213 in acetic acid at reflux afforded 4,7-dihydro-7-(1-phenyl-3-(substituted phenyl)-1H-pyrazol-4-yl)-5-phenyl-s-triazolo[1,5-a]pyrimidine 214 (Scheme 95).

$$\text{ArCHO} + \text{HN}_3\text{NNNNHN}_2 \xrightarrow{\text{AcOH}} \text{Ar}$$

$$\text{Ph}$$

$$\text{R}^1 = C_6H_5; \text{R}^2 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4.$$

Scheme 95. Synthesis of 7-(1H-pyrazol-4-yl)-5-phenyl-s-triazolo[1,5-a]pyrimidines 214.

Bhatt et al.\textsuperscript{197} reported the synthesis of 4,7-dihydro-[1,2,4]-triazolo[1,5-a]pyrimidine-6-carboxamides 215 via Biginelli reaction of 1-phenyl-3-aryl-1H-pyrazol-4-carboxaldehyde 2, 1H-1,2,4-triazol-3-amine 213 and acetoacetanilide derivatives 64 under conventional and microwave irradiation conditions (Scheme 96).

$$\text{ArCHO} + \text{HN}_3\text{NNNNHN}_2 \xrightarrow{i} \text{Ar}$$

$$\text{R}^1 = C_6H_5; \text{R}^2 = C_6H_5, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4; \text{R}^3 = H, CH_3, Br; \text{R}^4 = -CH_3, -HC(CH_3)_2.$$

Scheme 96. Synthesis of 4,7-dihydro-[1,2,4]-triazolo[1,5-a]pyrimidine-6-carboxamides 215.

3.2.1.3.3. Pyrazolo[3,4-d]pyrimidine derivatives. The reaction of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 111 with pyrazol-4-carboxaldehyde 2 in the presence of sodium acetate and PEG-400 as a solvent gave the corresponding 4-(arylidene)-3-methyl-1-phenyl-1H-pyrazol-5-ones 112. The reaction of 112 with guanidine hydrochloride 184 and sodium hydroxide in the presence of PEG-400 afforded the corresponding pyrazolo[3,4-d]pyrimidin-6-amine derivatives 216\textsuperscript{198} (Scheme 97).

$$\text{ArCHO} + \text{Ph}$$

$$\text{N}_3\text{N} \xrightarrow{\text{PEG-400}} \triangle$$

$$\text{H}_2\text{N}$$

$$\text{R}^1 = \text{CH}_3, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-F-C_6H_4; \text{R}^2 = \text{Cl}, \text{H}.$$

Scheme 97. Synthesis of pyrazolo[3,4-d]pyrimidin-6-amine derivatives 216.
3.2.1.1.4. Fused [5-6] system with five heteroatoms. 3.2.1.1.4.1. 1,2,4-Triazolo[4,3-b]1,2,4-triazine derivatives. Hamama et al.\textsuperscript{199} reported that the condensation of 4-amino-6-benzyl-3-hydrazone-1,2,4-triazine-5(4H)-one \textbf{217} with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde \textbf{2} afforded the corresponding Schiff bases \textbf{218}. Treatment of compound \textbf{218} with acetic anhydride gave \( N \)-acetyl-\( \text{N} \)-(2-acetyl-6-benzyl-3-[1,3-diphenyl-1H-pyrazol-4-yl]-7-oxo-2,3-dihydro-1,2,4-triazolo[4,3-b] 1,2,4-triazin-8(7H)-yl)acetamide \textbf{219} (Scheme 98).

![Scheme 98](image)

Scheme 98. Synthesis of 3-(1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]-1,2,4-triazin-8(7H)-ylacetamide \textbf{219}.

3.2.1.1.5. Fused [6-5] system with two heteroatoms. 3.2.1.1.5.1. Benzo[d]imidazole derivatives. Condensation of \( o \)-phenylenediamines derivatives \textbf{68} with pyrazole-4-carboxaldehydes \textbf{2} afforded the corresponding 2-(pyrazol-4-yl) benzo[d]imidazoles \textbf{220}\textsuperscript{195,200-204} (Scheme 99).

![Scheme 99](image)

Scheme 99. Synthesis of 2-(pyrazol-4-yl) benzo[d]imidazoles \textbf{220}.

3.2.1.1.5.2. Benzo[d]oxazole derivatives. Condensation of pyrazole-4-carboxaldehydes \textbf{2} with 2-aminophenol derivatives \textbf{221} under different conditions led to the formation of the corresponding benzo[d]oxazole derivatives \textbf{222}\textsuperscript{72,202,205} (Scheme 100).

![Scheme 100](image)

Scheme 100. Synthesis of benzo[d]oxazole derivatives \textbf{222}. 
3.2.1.5.3. **Benzo[d]thiazole derivatives.** The reaction of pyrazole-4-carboxaldehyde 2 with 2-aminobenzenethiol 223 in the presence of PCl₃ in ethanol afforded the corresponding benzo[d]thiazole 224\(^{202}\) (Scheme 101).

\[
\text{ArCHO} + \begin{array}{c}
\text{NH}_2 \\
223
\end{array} \xrightarrow{\text{PCl}_3 / \text{Ethanol}} \begin{array}{c}
\text{N} \\
224
\end{array} \xrightarrow{60 \degree C, 4h} \begin{array}{c}
\text{Ar} \\
80-87\%
\end{array}
\]

\(R^1 = C_6H_5, \text{Pyridin-2-yl}; R^2 = 2\text{-HO-}C_6H_4, C_6H_5.\)

**Scheme 101.** Synthesis of benzo[d]thiazoles 224.

3.2.1.6. **Fused [6-5] system with three heteroatoms.**

3.2.1.6.1. **Pyrano[2,3-c]pyrazole derivatives.** Pyrano[2,3-c]pyrazole derivatives 225 were prepared via the one-pot cyclocondensation reaction of pyrazolone 111, substituted pyrazole-4-carboxaldehydes 2 and malononitrile 53 in polyethylene glycol (PEG-400) as a green solvent\(^{206,207}\) or in ethanol at reflux in the presence of piperidine\(^{208}\) (Scheme 102).

\[
\begin{array}{c}
\text{Ph} \\
225
\end{array} \xrightarrow{i} \begin{array}{c}
\text{N} \\
R^1 \\
R^2
\end{array} \xrightarrow{i} \begin{array}{c}
\text{N} \\
R^3
\end{array} \xrightarrow{i} \begin{array}{c}
\text{N} \\
R^4
\end{array}
\]

\(R^1 = H, Cl; R^2 = C_6H_5, 4\text{-Br-}C_6H_4, 4\text{-H}_3C\text{-}C_6H_4, 4\text{-H}_3CO\text{-}C_6H_4, 4\text{-Cl-}C_6H_4, 4\text{-F-}C_6H_4, 4\text{-HO-}C_6H_4, 4\text{-O}_2N\text{-}C_6H_4, CH_3, 2\text{-Thienyl}; R^3 = H, C_6H_5; i = \text{PEG-400/ Stirr 40 \degree C 2hrs, EtOH/ Pip. / reflux.}\)

**Scheme 102.** Synthesis of pyrano[2,3-c]pyrazole derivatives 225.

Reaction of pyrazolone derivatives 111 with 2-((5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile 54 afforded the corresponding 6-amino-1-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles 226\(^{161,162}\). On the other hand, Abderazek et al.\(^{161}\) reported that heating of pyrazolone derivatives 111 with 54 in ethanol containing piperidine afforded a mixture of 6-amino-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles 227 and 1,7-diphenyl-4,7-dihydro-1H-pyrano[2,3-c;6,5-c9]dipyrazoles 228 (Scheme 103).
3.2.1.1.6.2. Pyrano[2,3-d]thiazole derivatives. Abdelrazek et al.\textsuperscript{161} reported that the reaction of 2-((5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile 54 with substituted thiazolin-4-ones 199 afforded pyrano[2,3-d]thiazole derivatives 229 but not thiazolo[3,2-\(a\)]pyridine derivatives 203 (Scheme 104).

\[ \text{Scheme 104. Synthesis of pyrano[2,3-d]thiazole derivatives 229.} \]

3.2.1.1.6.3. Thiopyrano[2,3-d]thiazole derivatives. Metwally et al.\textsuperscript{209} reported that the knöevenagel condensation of 3-phenyl-4-thioxo-2-thiazolidinone 230 with 1-phenyl-3-aryl-1H-pyrazole-4-carboxaldehydes 2 in glacial acetic acid at reflux or in PEG-400 at room temperature without a catalyst afforded the corresponding 5-pyrazolylmethylene derivatives 231. [4+2] Cycloaddition reaction of compounds 231 with acrylonitrile and ethyl acrylate 232 afforded the corresponding thiopyrano[2,3-d]thiazole derivatives 233 (Scheme 105).

\[ \text{Scheme 105. Synthesis of thiopyrano[2,3-d]thiazole derivatives 233.} \]
3.2.1.1.7. Fused [6-6] system with one heteroatom. 3.2.1.1.7.1. Chromene derivatives. Oxidative cyclization of pyrazolylpropenones 42 using copper chloride in DMSO\textsuperscript{105,210} or hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) in potassium hydroxide solution in methanol by Algar Flynn Oymanda (AFO) reaction\textsuperscript{211} gave chlorochromones 234 (Scheme 106).

![Diagram of chlorochromones 234 synthesis]

\[ R^1 = \text{C}_6\text{H}_5, \text{CH}_3; R^2 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, 4-\text{Br}-\text{C}_6\text{H}_4, 4-\text{O}_2\text{N}-\text{C}_6\text{H}_4, 4-\text{H}_3\text{CO}-\text{C}_6\text{H}_5, 4-\text{F}-\text{C}_6\text{H}_4; R^3 = \text{H}, \text{CH}_3; R^4 = \text{H}, \text{Cl}, \text{CH}_3, \text{Br}, \text{F}. \]

Scheme 106. Synthesis of chlorochromones 234.

El-Emary et al.\textsuperscript{166} reported that the treatment of hydrazone derivative 58 with salicylaldehyde 43 yielded chromene 235 (Scheme 107).

![Diagram of chromene 235 synthesis]


A series of 4-pyrazolyl-4\texttextit{H}-benzopyranes 237 has been synthesized via a one-pot three-component cyclocondensation reaction of 1-phenyl-3-(het)aryl-pyrazole-4-carboxaldehyde 2, malononitrile 53, and dimedone 236 in the presence of (diacetoxyiodo)benzene\textsuperscript{212} or piperidine as catalysts\textsuperscript{208} (Scheme 108).

![Diagram of 4-pyrazolyl-4\texttextit{H}-benzopyranes 237 synthesis]

\[ R^1 = \text{C}_6\text{H}_5; R^2 = \text{C}_6\text{H}_5, 4-\text{Br}-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, 4-\text{F}-\text{C}_6\text{H}_4, 4-\text{H}_3\text{CO}-\text{C}_6\text{H}_5, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{O}_2\text{N}-\text{C}_6\text{H}_4, 2-\text{Thienyl}; i = \text{i} \text{EtOH/} \text{excess} \text{CuCl}_2/ \text{EtOH/} \text{Pip.} \text{/reflux, KOH/ CH}_3\text{OH/} \text{H}_2\text{O}_2. \]

Scheme 108. Synthesis of 4-pyrazolyl-4\texttextit{H}-benzopyranes 237.

3.2.1.1.7.1.2. Quinoline derivatives. Multi-component reaction of pyrazole-4-carboxaldehydes 2, dimedone\textsuperscript{213-215} or 1,3-cyclohexanedione\textsuperscript{215} 236 and methyl-3-aminobut-2-enoate\textsuperscript{213} 238 or ethylacetoacetate\textsuperscript{214,215} 64 under various conditions afforded hexahydroquinoline derivatives 239 (Scheme 109).
Scheme 109. Synthesis of hexahydroquinoline derivatives 239.

Heating a mixture of pyrazole-4-carboxaldehyde 2, malononitrile 53, and the appropriate β-enaminones 240 in acetonitrile containing piperidine at reflux led to the formation of the corresponding 2-amino-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile 241. Moreover, the reaction of pyrazole-4-carboxaldehyde 2, Meldrum’s acid 242, and the appropriate β-enaminones 240 in acetonitrile containing few drops of piperidine at reflux afforded the corresponding 7,7-disubstituted-3,4,7,8-tetrahydroquinoline-2,5(1H,6H)-dione 243 (Scheme 110).

Scheme 110. Synthesis of hexahydroquinoline-3-carbonitriles 241 and tetrahydroquinoline-2,5-diones 243.

3.2.1.7.1.3. Isoquinoline derivatives. Nandakumar and Perumal reported that the coupling reactions of N-benzyl-1-(2-bromo-4,5-dimethoxyphenyl)methanamine 244, 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 and 1-ethynyl-2-phenoxybenzene 245 using copper(I) iodide (CuI) as a catalyst afforded propargyl amine derivative 246 which underwent intramolecular carbocyclization to give tetrahydroisoquinoline derivative 247 (Scheme 111).
Scheme 111. Synthesis of tetrahydroisoquinoline derivative 247.

3.2.1.8. Fused [6-6] system with two heteroatoms. 3.2.1.8.1. Quinazoline derivatives. Biginelli condensation of cyclohexane-1,3-dione\textsuperscript{120,219} or 5,5-dimethyl-1,3-cyclohexanedicione\textsuperscript{220} 236, (thiourea or urea 184) and pyrazole-4-carboxaldehyde 2 in methanol at reflux afforded 2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one or 4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione derivatives 248.\textsuperscript{120,219,220} Similarly, condensation of cyclohexanone 249, (thiourea or urea 184) and 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 in methanol at reflux afforded 3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione or 3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one analogues 250\textsuperscript{219} (Scheme 112).

Scheme 112. Synthesis of hexahydroquinazolin-5(1H)-ones and hexahydroquinazoline-2(1H)-thiones 248 and 250.

Kamble et al.\textsuperscript{68} reported the synthesis of 3-benzyl-2,3-dihydro-2-(1-phenyl-3-substituted-1H-pyrazol-4-yl)quinazolin-4(1H)-ones 252 via the reaction of 3-(substituted)-1-phenyl-1H-pyrazole-4-carboxaldehydes 2 with aminobenzamide 251 upon heating in methanol at reflux in the presence of potassium carbonate (Scheme 113).
R\textsuperscript{1} = C\textsubscript{6}H\textsubscript{5}; R\textsuperscript{2} = C\textsubscript{6}H\textsubscript{5}, 3-Br-C\textsubscript{6}H\textsubscript{4}, 4-Cl-C\textsubscript{6}H\textsubscript{4}, 4-F-C\textsubscript{6}H\textsubscript{4}, 4-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{4}, Pyridine-3-yl, Thiophen-2-yl.

**Scheme 113.** Synthesis of 3-benzyl-2-(1-phenyl-3-substituted-1H-pyrazol-4-yl)quinazolin-4(1H)-ones \textsuperscript{252}.

Nikpassand \textit{et al.}\textsuperscript{221} reported that pyrazolyl-substituted quinazolinones \textsuperscript{252} were obtained \textit{via} a three-component condensation of pyrazole-4-carboxaldehyde 2 with isatoic anhydride \textsuperscript{253} and ammonium acetate under microwave irradiation in the presence of [BDBIm] Br as a catalyst which could be recovered easily and reused without appreciable loss of reactivity (Scheme 114).

\[ \begin{align*}
\text{ArCHO} + \text{O} \rightarrow \text{NH}_2\text{OAc} & \rightarrow \text{NH}_2\text{N} \rightarrow \text{H}_3\text{N} \rightarrow \text{Z} \rightarrow \text{CH}_3 \\
2 & & & & 252 \\
& & & & \\
\text{[BDBIm] Br} = \text{H}_3\text{C} & \rightarrow & \text{N} & \rightarrow & \text{N} & \rightarrow & \text{Z} & \rightarrow & \text{CH}_3 \\
& & & & & & & & & \text{2Br} \\
& & & & & & & & & \text{R}^1 \rightarrow \text{C}_6\text{H}_5; \text{R}^2 = 4-\text{H}_3\text{CO}-\text{C}_6\text{H}_4, 4-\text{HO}-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, 2-\text{HO}-\text{C}_6\text{H}_4, \text{C}_6\text{H}_5. \\
\end{align*} \]

**Scheme 114.** Synthesis of pyrazolyl-substituted quinazolinones \textsuperscript{252}.

Mehta \textit{et al.}\textsuperscript{222} reported the synthesis of a series of quinazolin-4(3H)-one derivatives \textsuperscript{252} containing a (1,3-diphenyl-1H-pyrazol-4-yl) substituent at the position-2 and aromatic or heteroaromatic substituents at the position-3 by using \textit{l}-proline \textsuperscript{254} to catalyze the one-pot multi-component reaction of 1-phenyl-3-aryl-1H-pyrazole-4-carboxaldehyde 2, isatoic anhydride \textsuperscript{253}, aromatic amines \textsuperscript{77} in methanol at reflux (Scheme 115).

\[ \begin{align*}
\text{ArCHO} + \text{O} \rightarrow \text{NH}_2\text{OAc} + \text{Ar}^1\text{NH}_2 & \rightarrow \text{Ar}^1\text{N} \rightarrow \text{N} \rightarrow \text{N} \rightarrow \text{CH}_3 \\
2 & & & & & & & & 252 \\
& & & & & & & & 68-83\% \\
& & & & & & & & \text{Ar}^1 = \text{C}_6\text{H}_5, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{H}_3\text{CO}-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, 4-\text{Br}-\text{C}_6\text{H}_4, 4-\text{F}-\text{C}_6\text{H}_4, 4-\text{O}\textsubscript{2}\text{N}-\text{C}_6\text{H}_4, 4-\text{Pyr.} \\
\end{align*} \]

**Scheme 115.** Synthesis of pyrazolyl-substituted quinazolinones \textsuperscript{252}.

3.2.1.1.8.2. Phthalazine derivatives. The reaction of ethyl-5-cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate \textsuperscript{255} with pyrazolylmethylene malononitrile \textsuperscript{54} gave the phthalazinone derivative \textsuperscript{256}\textsuperscript{161,162} (Scheme 116).

\[ \begin{align*}
\text{Ar-NC} \rightarrow \text{C} \rightarrow \text{CN} & \rightarrow \text{C} \rightarrow \text{O} \rightarrow \text{EtO} \rightarrow \text{EtO} \rightarrow \text{N} \rightarrow \text{N} \rightarrow \text{Ph} \\
54 & & & & & & & & 255 \\
& & & & & & & & 256 \\
& & & & & & & & 76\% \\
& & & & & & & & \text{Ar} = \text{Ph}, \text{N}, \text{N} \rightarrow \text{Ph} \\
\end{align*} \]
Scheme 116. Synthesis of phthalazinone derivative 256.

3.2.1.9. Fused [6-6] system with three heteroatoms. 3.2.1.9.1. Pyridopyrimidine derivatives. Nia et al. reported that stirring equimolar amounts of 6-amino-2-(methylthio)pyrimidin-4(3H)-one 257, Meldrum’s acid 242, and pyrazole-4-carboxaldehydes 2 with a catalytic amount of 1,2–dimethyl-N-butanesulfonic acid imidazolium hydrogen sulfate [DMBSI]HSO₄ in an oil bath led to the formation of the corresponding pyridopyrimidine derivatives 258 (Scheme 117).

\[
\begin{align*}
&\text{NH}_2 \quad \text{O} \quad \text{HN}\text{Me} \\
&\text{257} \\
&\text{O} \quad \text{CO} \quad \text{C}_\text{Me} \text{C}_\text{H}_3 \\
&\text{242} \\
&\text{ArCHO} \\
&\text{2} \\
&\text{[DMBSI]HSO}_4 \\
&\text{80 °C} \\
&\text{Ar} = \text{C}_\text{6H}_5, 4-\text{H}_2\text{CO}-\text{C}_\text{6H}_4, 4-\text{Cl}-\text{C}_\text{6H}_4, 4-\text{O}_2\text{N}-\text{C}_\text{6H}_4, 3-\text{O}_2\text{N}-\text{C}_\text{6H}_4.
\end{align*}
\]

Scheme 117. Synthesis of pyridopyrimidine derivatives 258.

3.2.1.9.2. Benzo[e][1,4,2](ox/di/thi)azaphosphinine derivatives. Reaction of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 with 2-aminophenol 221, 1,2-phenylenediamine 68 and 2-aminothiophenol 223 in the presence of diethyl phosphite \(\text{H-P(O)(OEt)}_2\) 125 and sodium hydride gave 3-(1,3-diphenyl-1H-pyrazol-4-yl)-2-ethoxy-3,4-dihydrobenzo[e][1,4,2](ox/di/thi)azaphosphinine-2-oxide derivatives 259 (Scheme 118). ¹¹⁷

\[
\begin{align*}
&\text{ArCHO} \quad \text{H-P(O)(OEt)}_2 \\
&\text{2} \quad \text{221, 68, 223} \\
&\text{NaH, 70 – 80 °C} \\
&\text{16 – 20 h} \\
&\text{X = O, NH, S.} \\
&\text{Ar} = \text{Ph} \quad \text{Ar} = \text{Ph} \\
&\text{259} \\
&\text{83-92%}
\end{align*}
\]

Scheme 118. Synthesis of 3-(1H-pyrazol-4-yl)-3,4-dihydrobenzo[e][1,4,2](ox/di/thi)azaphosphinine-2-oxide derivatives 259.

3.2.1.10. Fused [6-6] system with four heteroatoms. 3.2.1.10.1. Pyrimido[4,5-d]pyrimidine derivatives. Suressh et al. reported that a four-component reaction of 6-amino-1,3-dimethyluracil 260, \(N,N\)-dimethylformamide dimethyl acetal 261, 1-phenyl-3-(4-substituted-phenyl)-4-formyl-1Hpyrazoles 2 and aromatic amines 77 in the presence of 1-butyl-3-methylimidazolium tetrachloroferrate [Bmim]FeCl₄ ionic liquid as a promoting medium gave pyrazolopyrimido[4,5-d]pyrimidines derivatives 262 (Scheme 119).
**Scheme 119.** Synthesis of pyrazolopyrimido[4,5-d]pyrimidines derivatives 262.

3.2.1.1.1. Fused [6-7] system with two heteroatoms. 3.2.1.1.1.1. Benzo[b][1,4]thiazepine derivatives. Karale et al.\textsuperscript{210} reported that the condensation of pyrazolylpropenones 42 with 2-aminothiophenol 223 in ethanol containing acetic acid at reflux gave benzothiazepines 263 (Scheme 120).

**Scheme 120.** Synthesis of benzothiazepines 263.

3.2.2. Pyrazole-substituted tricyclic system. 3.2.2.1. Fused [5-5-6] system with three heteroatoms. 3.2.2.1.1. Cyclopenta[b]pyrazolo[4,3-e]pyridine derivatives. Lipson et al.\textsuperscript{225} reported that heating of equimolar quantities of 3-methyl-1H-pyrazol-5-amine 204, pyrazole-4-carboxaldehyde 2, and cyclopentane-1,3-dione 264 in 2-propanol at reflux led to the formation of the corresponding 3-methyl-4,6,7,8-tetrahydrocyclopenta[b]pyrazolo[4,3-e]pyridin-5(2H)-one 265 (Scheme 121).


3.2.2.2. Fused [5-5-6] system with five heteroatoms. 3.2.2.2.1. Dipyrazolo[3,4-b:4′,3′-e]pyridine derivatives. Dawane et al.\textsuperscript{226} reported that the microwave irradiation of pyrazolone 111, pyrazole-4-carboxaldehydes 2, and ammonium acetate 78 dissolved in PEG-400 afforded the corresponding 3,5-dimethyl-1,7-diphenyl-1,4,7,8-tetrahydrodipyrzolo[3,4-b:4′,3′-e]pyridines 266 (Scheme 122).
Scheme 122. Synthesis of 1,4,7,8-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridines 266.

3.2.2.2. Dipyrazolo[1,5-a:3',4'-d]pyrimidine derivatives. Chobe et al.\textsuperscript{227} reported that condensation of 4-(arylidene)-3-methyl-1-phenyl-1H-pyrazol-5-ones 112 with 4-[(4-chlorophenyl)diazenyl]-3H-pyrazole-3,5-diamine 267 in PEG-400 afforded pyrazolo[1,5-a]pyrimidines 268 (Scheme 123).

Scheme 123. Synthesis of pyrazolo[1,5-a]pyrimidines 268.

3.2.2.3. Fused [5-6-5] system with three hetero atoms. 3.2.2.3.1. [1,3]Thiazolo[3,2-a]benzimidazole derivatives. One-pot three-component reaction of 1,3-dihydro-2H-benzimidazole-2-thione 269 with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 and chloroacetic acid 64 in glacial acetic acid and acetic anhydride in the presence of sodium acetate afforded 2-[1H-pyrazol-4-yl-methylene][1,3]thiazolo[3,2-a]benzimidazol-3(2H)-one 270\textsuperscript{228} (Scheme 124).


3.2.2.3.2. Pyrrolo[3',4':5,6]thiopyrano[2,3-d]thiazole derivatives. [4+2] Cycloaddition reaction of 5-pyrazolylmethylene derivatives 231 with N-arylmaleimides 271 in acetic acid at reflux afforded pyrrolo[3',4':5,6]thiopyrano[2,3-d]thiazole derivatives 272 (Scheme 125).\textsuperscript{209}
3.2.2.4. Fused [5-6-6] system with two heteroatoms. 3.2.2.4.1. Furo[2,3-f]chromene derivatives. Ashok et al.\textsuperscript{229} reported the synthesis of \{3-[2-(3-aryl-1-phenyl-1Hpyrazol-4-yl)vinyl]-7H-furo[2,3-f]chromen-2-yl\}-(4-bromophenyl) methanones \textbf{273} by the reaction of 2-bromo-1-(4-bromophenyl)ethanone \textbf{101} with 2-hydroxychalones \textbf{42} in acetone containing K\textsubscript{2}CO\textsubscript{3} under conventional heating, microwave irradiation or ultrasonication (Scheme 126).

\[
\begin{align*}
\text{42} + \text{101} \xrightarrow{\text{Anhydous K}_2\text{CO}_3, \text{dry acetone}} \text{273}
\end{align*}
\]

\(R^1 = \text{C}_6\text{H}_5; R^2 = \text{C}_6\text{H}_5, 4-\text{Br-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4, 4-\text{H}_3\text{CO-}\text{C}_6\text{H}_4, 4-\text{H}_3\text{C}_2\text{O-}\text{C}_6\text{H}_4, 3,4\text{-di-(H}_3\text{CO)}-\text{C}_6\text{H}_3, \text{Naphth}-2\text{-yl}; Ar^1 = 4-\text{Br-C}_6\text{H}_4; i = \text{Conventional 54-61\%; Ultrasound 64-74\%; MW 79-85\%}
\]

Scheme 126. Synthesis of \{3-[2-(1Hpyrazol-4-yl)vinyl]-7H-furo[2,3-f]chromen-2-yl\}-(4-bromophenyl) methanones \textbf{273}.

3.2.2.4.2. Pyrazolo[1,2-b]phthalazine derivatives. Shaikh et al.\textsuperscript{230} prepared 3-amino-5,10-dioxo-1-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile \textbf{275} by the reaction of 1-phenyl-3-(p-tolyl)-1H-pyrazole-4-carboxaldehyde \textbf{2}, malononitrile \textbf{53} and phthalhydrazide \textbf{274} catalyzed by 20 mol\% of tributylammonium sulfate [Bu\textsubscript{3}NH][HSO\textsubscript{4}] under solvent-free condition (Scheme 127).

\[
\begin{align*}
\text{ArCHO} + \text{NC}_2\text{CN} + \text{274} \xrightarrow{[\text{Bu}_3\text{NH}][\text{HSO}_4], \text{solvent-free}} \text{275}
\end{align*}
\]

\(R^1 = \text{C}_6\text{H}_5; R^2 = 4-\text{H}_3\text{C}-\text{C}_6\text{H}_4.
\]

Scheme 127. Synthesis of 1-(1H-pyrazol-4-yl)-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile \textbf{275}.

3.2.2.4.3. Pyrrolo[1,2-a]quinolines derivatives. Kamal et al.\textsuperscript{231} reported that heating of 1-(2-aminophenyl)pyrrole \textbf{276}, pyrazole-4-carboxaldehydes \textbf{2}, and sulfamic acid \textbf{277} in H\textsubscript{2}O at reflux afforded dihydropyrrolo[1,2-a]quinolines derivatives \textbf{278} (Scheme 128).
3.2.2.5. Fused [6-5-5] System with Five Heteroatoms. 3.2.2.5.1. Pyrano[2,3-c:6,5-c']dipryazole Derivatives. Abdelrazek et al.\textsuperscript{161} reported that the reaction of two equivalents of 2-phenyl-2,4-dihydro-3H-pyrazol-3-ones \textsuperscript{111} with 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde \textsuperscript{2} afforded the corresponding 1,7-diphenyl-4,7-dihydro-1H-pyrano[2,3-c:6,5-c']dipryazoles \textsuperscript{279} (Scheme 129).

\begin{equation}
\begin{aligned}
\text{ArCHO} + \begin{array}{c}
\text{PhN} \\
\text{N}
\end{array} & \rightarrow \begin{array}{c}
\text{PhN} \\
\text{N}
\end{array} \\
2 & \text{276}
\end{aligned}
\end{equation}

\begin{equation}
\begin{aligned}
\text{H}_2\text{NSO}_3\text{H} & \text{277} \\
\text{Water, reflux} & \text{40-60 min}
\end{aligned}
\end{equation}

\begin{equation}
\begin{aligned}
\text{PhN} & \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \\
\text{R} = \text{C}_6\text{H}_5, \text{4-F-C}_6\text{H}_4, \text{4-Cl-C}_6\text{H}_4, \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{3,4,5-tri-H}_3\text{CO-C}_6\text{H}_2.
\end{aligned}
\end{equation}

Scheme 128. Synthesis of dihydropyrrolo[1,2-a]quinoxalines derivatives \textsuperscript{278}.

Scheme 129. Synthesis of 1,7-diphenyl-4,7-dihydro-1H-pyrano[2,3-c:6,5-c']dipryazoles \textsuperscript{279}.

3.2.2.6. Fused [6-5-6] System with One Heteroatom. 3.2.2.6.1. Indeno[1,2-b]Pyridine Derivatives. Mamaghani et al.\textsuperscript{215} reported that heating a mixture of 3-aryl-4-formylpyrazole \textsuperscript{2}, indanedione \textsuperscript{280}, ethyl acetoacetate \textsuperscript{64}, and ammonium acetate \textsuperscript{78} in the presence of cellulose-sulfuric acid in ethanol at reflux furnished 4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylates \textsuperscript{281} (Scheme 130).

\begin{equation}
\begin{aligned}
\text{ArCHO} + \begin{array}{c}
\text{CHO} \\
\text{Cl}
\end{array} & \rightarrow \begin{array}{c}
\text{CHO} \\
\text{Cl}
\end{array} \\
2 + \text{111} & \rightarrow \text{279}
\end{aligned}
\end{equation}

\begin{equation}
\begin{aligned}
\text{R} = \text{CH}_3, \text{C}_6\text{H}_5.
\end{aligned}
\end{equation}

Scheme 130. Synthesis of 4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylates \textsuperscript{281}.

3.2.2.7. Fused [6-5-6] System with Two Heteroatom. 3.2.2.7.1. Indeno[1,2-d]Pyrimidin Derivatives. Fahmy et al.\textsuperscript{120} reported that the reaction of 1,3-indanedione \textsuperscript{280} with urea or thiourea \textsuperscript{184} and pyrazole-4-carboxaldehydes \textsuperscript{2} gave indeno[1,2-d]pyrimidine-2-oxo(thioxo) derivatives \textsuperscript{282} (Scheme 131).

3.2.2.8. Fused [6-6-6] system with one heteroatom. 3.2.2.8.1. Acridine derivatives. The reaction of pyrazole-4-carboxaldehydes 2, dimeredone\textsuperscript{232,233} or 1,3-cyclohexanedione\textsuperscript{233} 236, NH\textsubscript{4}OAc 78 and a catalytic amount of magnetic iron oxide nanocrystals (nano Fe\textsubscript{3}O\textsubscript{4}) in a water bath under ultrasound irradiation\textsuperscript{232} or using environmentally friendly poly(4-vinylpyridinium)hydrogen sulfate P-(4-VPH)HSO\textsubscript{4} as a catalyst in aqueous medium\textsuperscript{233} afforded the corresponding 3,4,6,7,9,10-hexahydroacridine-1,8(2\textsubscript{H},5\textsubscript{H})-dione derivatives 283 (Scheme 132).

Scheme 132. Synthesis of 3,4,6,7,9,10-hexahydroacridine-1,8(2\textsubscript{H},5\textsubscript{H})-dione derivatives 283.

3.2.2.8.2. Benzo[h]chromene and benzo[f]chromene. Thumar and Patel\textsuperscript{208} reported the synthesis of a series of 4-pyrazolyl-4H-naphthopyran derivatives 285 and 286 by one-pot three-component cyclocondensation reactions of pyrazole-4-carboxaldehydes 2, malononitrile 53, and naphthols 284a or 284b, respectively, in the presence of piperidine as a catalyst (Scheme 133).

Scheme 133. Synthesis of 4-pyrazolyl-4H-naphthopyran derivatives 285 and 286.
3.2.2.8.3. Xanthene derivatives. Neena et al.\textsuperscript{234} reported that heating of 1-phenyl-3-aryl-1H-pyrazole-4-carboxaldehyde 2 with two equivalents of dimedone 236 in ethanol solution containing a catalytic amount of concentrated HCl at reflux afforded 3,3,6,6-tetramethyl-9-(3-aryl-1-phenyl-1H-pyrazol-4-yl)3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-diones 287 (Scheme 134).

\[
\text{ArCHO} + 2 \xrightarrow{\text{Conc. HCl, EtOH, Reflux}} \text{287}
\]

R = H, CH₃, OCH₃, Br, NO₂.

Scheme 134. Synthesis of 9-(3-aryl-1-phenyl-1H-pyrazol-4-yl)hexahydro-1H-xanthene-1,8(2H)-diones 287.

3.2.2.9. Fused [6-6-6] system with two heteroatoms. 3.2.2.9.1. Naphtho[1,2-e][1,3]oxazine derivatives. Abou-Elmagd and Hashem\textsuperscript{235} reported the preparation of 1-amidoalkyl-2-naphthols 288 via a one-pot condensation reaction of 1,3-diphenyl-pyrazole-4-carboxaldehyde 2, naphthalen-2-ol 284b and amides 184 in the presence of anhydrous zinc chloride under solvent-free conditions. Ring closure of 288 in ethanol at reflux gave the pyrazol-4-yl-naphtho[1,2-e][1,3]oxazine derivatives 289. On the other hand, the reaction of 2-naphthol 284b with two mole equivalents of 1,3-diphenyl-pyrazole-4-carboxaldehyde 2, and ammonia solution gave 1,3-bis(1,3-diphenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine 290 (Scheme 135).

\[
\text{284b} + \text{ArCHO} + \text{R}^\text{CONH}_2 \xrightarrow{\text{Abs. EtOH, reflux}} \text{288}
\]

85-90%

\[
\text{289}
\]

51-59%

R = NH₂, CH₃, C₆H₅.

Scheme 135. Synthesis of pyrazol-4-yl-naphtho[1,2-e][1,3]oxazine derivatives 289 and 290.

3.2.2.9.2. Pyrano[3,2-c]chromene derivatives. Heating of 4-hydroxy coumarin 291 with substituted pyrazole-4-carboxaldehydes 2 and malononitrile 53 in ethanol at reflux in the presence of piperidine as base catalyst afforded 2-amino-4- (3-(4-substituted)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitriles 292\textsuperscript{172} (Scheme 136).
Scheme 136. Synthesis of (1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyran[3,2-c]chromene-3-carbonitriles 292.

3.2.2.9.3. Chromeno[4,3-b]pyridine derivatives. Reddy and Rao\(^{236}\) reported that the reaction of pyrazole-4-carboxaldehydes 2 with chroman-4-one 293 gave \(\alpha,\beta\)-unsaturated ketone system 294. Initial Michael addition of phenacylpyridinium bromide 101 with compound 294 gave 1,5-dicarbonyl system 295 which subsequently underwent cyclization in the presence of NH\(_4\)OAc/ acetic acid to give chromeno[4,3-b]pyridines 296 (Scheme 137).

\[
\text{ArCHO} + \begin{array}{c}
\text{293} \\
\text{291}
\end{array} \xrightarrow{\text{Ethanol, piperidine, reflux, 4 h}} \begin{array}{c}
\text{292} \\
\text{53}
\end{array}
\]

\(R = 4\text{-HO-C}_6\text{H}_4, 4\text{-F-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 4\text{-O}_2\text{N-C}_6\text{H}_4, 4\text{-H}_2\text{N-C}_6\text{H}_4.\)


3.2.2.10. Fused [6-6-6] system with three heteroatoms. 3.2.2.10.1. Thiochromeno[3,4-d]pyrimidine derivatives. Suresh et al.\(^{237}\) reported the synthesis of thiochromeno[3,4-d]pyrimidine derivatives 298 via a one-pot three-component reaction of thiochrome-4-one 297, pyrazole-4-carboxaldehydes 2, and thiourea 184 in the presence of 1-butyl-3-methylimidazolium hydrogen sulfate [Bmim]HSO\(_4\) (Scheme 138).

\[
\text{ArCHO} + \begin{array}{c}
\text{297} \\
\text{184}
\end{array} \xrightarrow{[\text{Bmim}]\text{HSO}_4, 70^\circ \text{C, 1-2h}} \begin{array}{c}
\text{298} \\
\text{84%}
\end{array}
\]

\(\text{Ar} = \text{Pyrazole, 4-O}_2\text{N-Pyrazole, 4-Cl-Pyrazole, 4-H}_3\text{CO-Pyrazole.}\)

3.2.2.10.2. **Pyrimido[4,5-b]quinoline derivatives.** Jourshari et al.\textsuperscript{238} reported that 5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-4,6(3H,7H)-dione derivatives \textsuperscript{299} were synthesized by one-pot three-component reaction of pyrazole-4-carboxaldehydes 2, dimedone or cyclohexanedione 236 and 6-amino-2-(methylthio)pyrimidin-4(3H)-one 257 in ethanol under ultrasonic irradiation in excellent yields (94-99\%) (Scheme 139).

\[
\text{R} = \text{H, CH}_3; \text{R}_1 = \text{C}_6\text{H}_5, \text{4-Cl-C}_6\text{H}_4, \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{4-O}_2\text{N-C}_6\text{H}_4, \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{4-Br-C}_6\text{H}_4.
\]

Scheme 139. Synthesis of tetrahydropyrimido[4,5-b]quinoline-4,6(3H,7H)-dione derivatives 299.

3.2.2.11. **Fused [6-6-6] system with five heteroatoms.** 3.2.1.2.11. **Pyrido[2,3-d:6,5-d']dipyrimidine derivatives.** Abdel-Aziem et al.\textsuperscript{239} reported that the reaction of two equivalents of 6-aminothiouracil 260 with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 in methanol containing few drops of hydrochloric acid led to the formation of 5-(1,3-diphenyl-1H-pyrazol-4-yl)-2,8-dithioxo-2,3,5,8,9,10-hexahydropyrido [2,3-d:6,5-d']dipyrimidin-4,6(1H,7H)-dione 300 (Scheme 140).

\[
\text{Scheme 140. Synthesis of 5-(1H-pyrazol-4-yl)hexahydropyrido [2,3-d:6,5-d']dipyrimidin-4,6(1H,7H)-dione 300.}
\]

3.2.3. **Pyrazole-substituted tetracyclic system.** 3.2.3.1. **Fused [6-5-6-6] system with two heteroatoms.**

3.2.3.1.1. **Benzo[g]thieno[3,4-b]thiochromene derivatives.** Metwally et al.\textsuperscript{209} reported that [4+2] cycloaddition reaction of 5-pyrazolylmethylene derivatives 231 with 1,4-naphthoquinone 301 afforded benzo[g]thieno[3,4-b]thiochromenes 302 (Scheme 141).

\[
\text{R} = \text{C}_6\text{H}_5, \text{4-H}_3\text{C}_6\text{H}_5, \text{4-H}_3\text{CO-C}_6\text{H}_4, \text{4-Cl-C}_6\text{H}_5.
\]

Scheme 141. Synthesis of benzo[g]thieno[3,4-b]thiochromenes 302.
3.2.3.2. Fused [6-5-6-6] system with four heteroatoms. 3.2.3.2.1. Imidazo[4,5-f][1,10]phenanthroline derivatives. Liu et al.\textsuperscript{240} reported that heating a mixture of 1,10-phenanthroline-5,6-dione 303, ammonium acetate 78 and pyrazole-carboxaldehydes 2 in glacial acetic acid gave Imidazo[4,5-f][1,10]phenanthroline derivatives 304 (Scheme 142).

\[ \text{Imidazo[4,5-f][1,10]phenanthroline derivatives 304} \]

\[ \text{R}^1 = 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3C-C_6H_4; \text{R}^2 = \text{H, CH}_3, -H_2C-C_6H_5, -(H_2C)_3-N(CH_3)_2, 2,4-O_2N-C_6H_4, 6-chloropyridazin-3-yl. \]

**Scheme 142.** Synthesis of Imidazo[4,5-f][1,10]phenanthroline derivatives 304.

3.2.4. Pyrazole-substituted pentacyclic system. 3.2.4.1. Fused [6-5-5-6-6] system with nine heteroatoms. 3.2.4.1.1. Pyrido[2,3-d:6,5-d']ditriazolopyrimidine derivatives. Abdel-Aziem et al.\textsuperscript{239} reported that the reaction of hexahydropyrido[2,3-d:6,5-d']dipyrimidine-4,6(1H,7H)-dione 300 with hydrazonoyl halides 105 in boiling chloroform gave ditriazolo[4,3-a]pyrimidin-5(1H)-one-dihydropyridine 305. Compound 305 was alternatively obtained by the reaction of ethyl-7-amino-5-oxo-1-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate 306 with 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde 2 in the presence of hydrochloric acid (Scheme 143).

**Scheme 143.** Synthesis of ditriazolo[4,3-a]pyrimidin-5(1H)-one-dihydropyridines 305.

**Conclusions**

Heterocycles, in particular nitrogen-containing heterocycles, have been found to show a range of important applications in various fields. Among the different nitrogen-containing heterocycles, pyrazole derivatives are the most active class of five-member heterocycles due to their wide variety of important applications. This review highlighted the different synthetic methods for the preparation of pyrazole-carboxaldehydes and their
utility as versatile precursors for various pyrazole-substituted heterocyclic systems as hybrid molecules. The heterocyclic compounds described in this review are arranged on the basis of the size of the heterocyclic ring as well as the location and number of heteroatoms. We hope that this analysis will be useful not only for synthetic organic chemists, but also for researchers interested in medicinal and biological chemistry.

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