SECTION I
1.1 INTRODUCTION

1.1.1 Carbonyl compounds and their reactivity pattern

Carbonyl compounds are extremely important class of organic compounds due to their easy accessibility, scope of applicability and high reactivity. The synthetic utility of carbonyl compounds is well known for more than a century. That is why these compounds are the backbone of organic chemistry. Among the carbonyl compounds, aldehydes and ketones are very important, particularly for their synthetic utility. All aldehydes and ketones contain a C=O bond, which is polar and electrons are attracted towards the oxygen atom.

\[
\begin{align*}
\text{O} &\quad \text{C} \quad \text{O} \\
\text{O} &\quad \text{C} \quad \text{O}
\end{align*}
\]

The oxygen atom combines with electrophiles and carbon atom combines with nucleophiles (Fig. 1.1).

Carbonyl compounds can be placed in one of two groups - those that contain a group that can be replaced by another group (Class I), and those that do not contain a group that can be replaced by another group (Class II).

In the following description an effort has been made to present important reactions of these classes (I \& II) of compounds along with effect of structure on reactivity which is followed
by a short review on the synthetically useful transformations starting from pyrazole-4-carbaldehydes.

**Carbonyl Compounds I:** Reactions of carboxylic acids and their derivatives with nucleophiles.

When a nucleophile attacks the carbonyl group of a carboxylic acid derivative, the carbon-oxygen $\pi$ bond breaks. The resulting intermediate is called a tetrahedral intermediate because the trigonal ($sp^2$) carbon in the reactant has become a tetrahedral ($sp^3$) carbon in the intermediate.

![Tetrahedral intermediate](image)

The tetrahedral intermediate formed by the nucleophilic attack on the carbonyl carbon of a carboxylic acid derivative ($Y = \text{OH, OR, NH}_2$, etc.) is not stable and cannot be isolated. It is not a final product and it is an intermediate formed on the way to the final product. A pair of non-bonding electrons on the oxygen re-forms the $\pi$ bond, and $Y^-$ will be expelled with its bonding electrons. For carboxylic acids and their derivatives much better leaving groups are available and acyl substitution predominates. It is thus the nature of $Y$ that determines whether a nucleophilic attack at a carbon-heteroatom multiple bond will lead to substitution or addition.

**Carbonyl Compounds II:** Reactions of aldehydes and ketones, and $\alpha,\beta$-unsaturated carbonyl compounds with nucleophiles.

i) **Reactions of aldehydes and ketones with nucleophiles**

These compounds mainly undergo three types of reactions:
1. **Nucleophilic addition reactions of aldehydes and ketones**

This is one of the most significant reactions of the carbonyl compounds. The mechanistic study of these reactions is much simpler than that of the addition to carbon-carbon multiple bonds. In most cases, it is the nucleophile (Nu') that forms the first new bond to carbon, and these reactions are regarded as nucleophilic additions.

![Chemical structure](image)

The electrophile shown in *step 2* is generally proton. It can be seen that *step 1* is exactly the same as *step 1* of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon. But the groups (R, R'= H, alkyl aryl, etc.) linked to carbonyl group are poor leaving groups. Thus, substitution does not compete with addition.

2. **α-Substitution reactions of aldehydes and ketones**

α-Substitution reactions involve substitution of a hydrogen atom by another group, at the carbon atom next to the C=O bond through intermediate enols or enolate ions. The functionalization of carbonyl compounds at α-carbon represents the most typical reaction of electrophilic substitution.

![Chemical structure](image)

*Formation of an enol and reaction with an electrophile*
Formation of an enolate ion and reaction with an electrophile

3. Condensation reactions

Aldehydes and ketones react with primary amines (R-NH₂) and with other ammonia derivatives (Z-NH₂) to form imines. An imine is a compound with a carbon-nitrogen double bond.

Compounds such as hydroxylamine (NH₂OH), hydrazine (NH₂NH₂), semicarbazide (NH₂NHCONH₂), and primary amines are all derivatives of ammonia because each has a substituent in place of one of the hydrogens of ammonia (NH₃). The imine obtained from the reaction of a carbonyl compound and a primary amine is called a Schiff base; the imine obtained from the reaction with hydroxylamine is called an oxime; imine obtained from the reaction with semicarbazide is called a semicarbazone; the imine obtained from the reaction with hydrazine is called a hydrazone.

In carbonyl-carbonyl condensation reactions, two carbonyl molecules react to form a single organic product together with a molecule of water. Reactions of two molecules of the same aldehyde or ketone are called aldol condensations.
ii) Reactions of α,β-unsaturated carbonyl compounds

The contributing resonance structures for an α,β-unsaturated carbonyl compound shows that the molecule has two electrophilic sites – the carbonyl carbon and the β-carbon.

This means that if an aldehyde or ketone has a double bond in the α,β-position, a nucleophile can add either to the carbonyl carbon or to the β-carbon. Nucleophilic addition to the carbonyl carbon is called direct addition or 1,2-addition.

**Direct addition**

Nucleophilic addition to the β-carbon is called conjugate addition, because addition occurs across the conjugated system. This conjugate addition is also called 1,4-addition.
Conjugate addition

\[
\text{Nu}^- + \text{ROH} \rightarrow \text{Nu-R-OH} + \text{H}_2\text{O}
\]

Effect of Structure on Reactivity

It is well-established that the nature of substituent greatly affects the reactivity of carbonyl compounds towards nucleophilic addition reaction. An alkyl group, being electron-donating, would decrease the positive character of the carbonyl carbon and thus makes it less susceptible to nucleophilic attack, and second, the sheer bulk of an alkyl group presents greater steric hindrance than a smaller hydrogen atom to the approaching nucleophile. On these considerations, we anticipate decreasing reactivity with increasing alkyl substitution as displayed by the following series:

\[
\begin{align*}
\text{H} & \quad > \quad \text{H} & \quad > \quad \text{R} \\
\text{C}=\text{O} & \quad > \quad \text{C}=\text{O} & \quad > \quad \text{C}=\text{O}
\end{align*}
\]

As may be expected electron-withdrawing α-substituents such as –NO₂ or halogen would increase the positive character of the carbonyl carbon and thus facilitate the attack of nucleophiles.

Out of aldehydes and ketones, aldehydes are more reactive than ketones due to both steric and electronic factors. The substituent around the carbonyl group may be H, alkyl, aryl, and hetaryl.
Aryl groups are somewhat deactivating as compared to alkyl, because delocalized π orbitals of the ring act as an electron source (resonance stabilization).

Literature reports reveal that heteroaromatic aldehydes behave quite differently than alkyl or arylaldehydes. Jurcsak et al. observed unusual reactivity of 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde in base-catalysed aldol reactions with acetophenone (Scheme 1.1).

Scheme 1.1
Previous studies from our research group have shown that pyrazole aldehydes 5, which are easily accessible through Vilsmeier-Haack reaction\(^2\) of ketone hydrazones 4 can act as useful precursor for the synthesis of a variety of heterocyclic compounds of potential medicinal interest (Scheme 1.2).

\[
\begin{array}{c}
\text{Ar} = \text{C}_6\text{H}_5; 4-\text{CH}_3\text{C}_6\text{H}_4; 4-\text{NO}_2\text{C}_6\text{H}_4; 4-\text{FC}_6\text{H}_4; \\
4-\text{ClC}_6\text{H}_4; 4-\text{BrC}_6\text{H}_4; 4-\text{OCH}_3\text{C}_6\text{H}_4
\end{array}
\]

**Scheme 1.2**

It has been observed that the presence of pyrazole moiety has great influence on the reactivity of aldehydic group and in certain cases it is not possible to perform common transformations of aldehydes using standard conditions. In such cases some modifications in the reaction conditions are required. Apart from reported work from other research groups, some recent examples from our research group are also illustrative. While exploring the chemistry of α,β-chalcone ditosylate, it has been found that the reaction of 1,3-diaryl-2,3-ditosyloxypropanones (6) with KOH/ MeOH affords the desoxybenzoin 7 (Scheme 1.3).\(^3\)

\[
\begin{array}{c}
\text{R} = \text{H}, \text{CH}_3, \text{OCH}_3, \text{Cl}, \text{Br}
\end{array}
\]

**Scheme 1.3**

On the other hand using similar conditions, the 1-phenyl-3-(3-aryl-1-phenyl-4-pyrazolyl)-2,3-ditosyloxypropanone (8a) affords the elimination product 8b (Scheme 1.4).\(^4\)
Scheme 1.4

It can be anticipated that the presence of 1,3-diaryl-4-pyrazolyl group in place of phenyl might inhibit 1,2-shift, and thus allows alternative reaction \textit{i.e.}, elimination reaction.

Goldsmith has reported the preparation of chalcone dichlorides by the addition of chlorine to phenyl styrylketones.\(^5\) Weber \textit{et al.} have reported the synthesis of \textit{erythro} 2,3-dichloro-1,3-diarylpropan-1-ones by the reaction of PhICl\(_2\) with chalcones.\(^6\) Keeping in view of these studies, the reaction of 1-aryl-3-(3-aryl-1-phenyl-4-pyrazolyl)prop-2-en-1-ones (chalcone analogs) (9a) with (dichloroiodo)benzene in dichloromethane was performed in our lab to obtain corresponding dichlorides.

To determine the fate of this proposal, 9a (Ar = Ph, Ar' = Ph) has been treated with PhICl\(_2\) in DCM. The single product isolated from this reaction was characterized as 1-phenyl-3-(1,3-diphenyl-4-pyrazolyl)-2-chloro-prop-2-en-1-one (9b) (Scheme 1.5).\(^4\)
1.1.2 Pyrazole-4-carbaldehydes as useful precursors in organic synthesis (A review)

A literature survey reveals that a number of biologically active compounds have been synthesized using pyrazole-4-carbaldehydes, which exhibit various medicinal properties such as antitumor, antiangiogenesis, and antiviral activity\textsuperscript{7-9}.

The above facts, prompted us to further extend the reactions of pyrazole-4-carbaldehydes for the synthesis of various biologically potent molecules. Before discussing the results of experimental work, it is desirable to review reported work on some organic syntheses starting from pyrazole-4-carbaldehydes. The review presented here is classified into three categories, A-C, depending upon the type of reactions:

A. Addition and reduction

1,3-Diarylpyrazol-4-ylacetic acids (11), which are known anti-inflammatory and thrombocyte aggregation inhibitors, are prepared by reaction of 1,3-diaryl-1\textit{H}-pyrazole-4-carbaldehydes (5) with HCN (prepared \textit{in situ} from NaCN or KCN and an organic or inorganic acid) in a polar solvent (DMF, 2-PrOH, 2-BuOH), to give aldehyde cyanohydrins 10, followed by reduction with SnCl\textsubscript{2} in HCl-AcOH (Scheme 1.6)\textsuperscript{10,11}

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{N} \\
\text{CHO} & \quad \text{Ar} \\
\uparrow \text{>1.2 equiv HCN/DMF} & \quad \text{SnCl}_{2}/\text{HCl-AcOH} \quad \text{(63-78\%)} \\
\text{Ph} & \quad \text{N} \quad \text{N} \\
\text{HO} & \quad \text{CN} \\
\text{Ar} \quad & \quad \text{COOH} \\
\text{10} & \quad \text{11}
\end{align*}
\]

\textbf{Scheme 1.6}

Ar = Ph, 4-ClC\textsubscript{6}H\textsubscript{4}, 4-FC\textsubscript{6}H\textsubscript{4}, 4-BrC\textsubscript{6}H\textsubscript{4}, 4-MeOC\textsubscript{6}H\textsubscript{4}, 4-MeC\textsubscript{6}H\textsubscript{4}

3-Aryl-1-phenyl-1\textit{H}-pyrazole-4-carbaldehydes (5) have been reduced with sodium borohydride under mild conditions to give hydroxymethylpyrazoles 12 which are converted into the corresponding 4-chloromethyl derivatives 13 by treatment with thionyl chloride. The subsequent reaction with triphenylphosphine has led to the formation of triphenyl(4-
pyrazolylmethyl)phosphonium chlorides (14), and Wittig reaction of the later with aromatic or heteroaromatic aldehydes yields 4-(2-arylethenyl)pyrazoles (15) (Scheme 1.7).\(^{12}\)

\[
\begin{align*}
\text{Ph} & \quad \text{NaBH}_4 \quad \text{Ph} \\
\text{CHO} & \quad 11 \quad \text{SOCl}_2 \quad 12 \quad \text{PPh}_3 \\
\text{N} - \text{N} & \quad \text{CH}_2 \text{OH} \quad \text{CH}_2 \text{Cl} \\
\text{Ar} & \quad 13 \\
\text{Ar} \quad \text{(Het)} \text{Ar} & \quad \text{CHO} \\
\text{Ar} & \quad 15
\end{align*}
\]

\(\text{Ar = Ph, 4-ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2\text{-thienyl; Ar} = 4-\text{NO}_2\text{C}_6\text{H}_4, 5-\text{NO}_2\text{-2-furyl}\)

Scheme 1.7

**B. Oxidation**

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde (16) on oxidation with potassium permanganate affords pyrazole-4-carboxylic acid (17), which is converted to corresponding ethyl ester 18 by reaction with ethanol in acidic medium (Scheme 1.8).\(^{13}\)

\[
\begin{align*}
\text{R} & \quad \text{CHO} \quad \text{R} \quad \text{CO}_2\text{H} \quad \text{R} \quad \text{CO}_2\text{Et} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{Ph} & \quad 16 \quad \text{PTC} \quad 17 \quad \text{EtOH, H}^+ \\
\text{Cl} & \quad \text{Cl} \quad \text{Cl}
\end{align*}
\]

\(\text{R} = 4\text{-pyridyl}\)

Scheme 1.8

3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5) have also been cleanly oxidized by potassium permanganate in water-pyridine medium to afford the corresponding acids 19 in high yield, which have been converted into the corresponding chlorides 20 and amides 21 as depicted in Scheme 1.9.\(^{14}\)
Abu-Zaied et al. reported the synthesis of pyrazolylloxadiazoles (25). Their synthesis involves conversion of 3-substituted-1-phenyl-1H-pyrazole-4-carbaldehydes (5) to 1,3,4-oxadiazole derivatives 25 by oxidation using acidic K$_2$Cr$_2$O$_7$ followed by esterification to pyrazole esters 22, which reacts with hydrazine to give hydrazides 23. Finally, compounds 23 have been converted to pyrazolylloxadiazole 24 on reaction with carbon disulphide in KOH solution. Pyrazolylloxadiazoles 24 on reaction with alkyl bromides or halosugars in the presence of basic medium produce alkylated product 25 (Scheme 1.10).

\[ R^1, R^2, R^3 = \text{aryl, hetaryl} \]
C. Condensation reactions

Reactions with active methylene compounds. 1,3,5,6-Tetrasubstituted pyrazolo[3,4-\(b\)]pyridines (27-30) have been synthesized by Friedländer condensation of 5-aminopyrazole-4-carbaldehydes (26), with active methylene compounds such as ketones, malononitrile, phenyl acetonitrile, and cyanoacetamide, respectively, in alcoholic potassium hydroxide as a basic catalyst (Scheme 1.11).\textsuperscript{16-18}

![Scheme 1.11](image)

3-Aryl-1-phenyl-1\(H\)-pyrazole-4-carbaldehydes (5) undergo aldol condensation reactions with methyl ketones to give diaryl pyrazolylpropenones 31. Chalcones 31 exhibit
cyclocondensation with phenylhydrazine to give pyrazolyl pyrazoline derivatives 32 useful as potential components of luminescent composite dyes (Scheme 1.12).^{19}

![Scheme 1.12](image)

R = Ph, 3-pyridyl, 2-thienyl, 5-Me-2-furyl
R$^1$ = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-EtC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl, 2-furyl

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazole-4-carbaldehyde (33) has been allowed to react with different reagents such as aromatic ketones and hippuric acid to afford $\alpha,\beta$-unsaturated ketones 34, and 5-oxazolones 35, respectively (Scheme 1.13).^{13}

![Scheme 1.13](image)

R = 4-pyridyl; Ar = Ph, 4-MeC$_6$H$_4$
2,4-Dichloro-5-fluoroacetophenone \((36)\) reacts with 1,3-diphenyl-1\(H\)-pyrazole-4-carbaldehyde \((5)\) to give 1-(2,4-dichloro-5-fluorophenyl)-3-(1,3-diphenyl-1\(H\)-pyrazol-4-yl)prop-2-en-1-one \((37)\) (Scheme 1.14).\(^{20}\)

![Scheme 1.14](image)

The reaction of 1,3-diaryl-1\(H\)-pyrazole-4-carbaldehydes \((5)\) with various substituted acetophenones in methanol in the presence of EtONa affords the corresponding \(\alpha,\beta\)-unsaturated ketones \((38)\) in good yields. Refluxing \((38)\) with different phenacyl pyridium bromides in acetic acid in the presence of ammonium acetate gives pyridinylpyrazoles \((39)\) (Scheme 1.15).\(^{21}\)

![Scheme 1.15](image)

2-Aminopyrimidothiazolo[4,5-\(b\)]quinoxalin-4-one \((41)\) has been utilized as a key intermediate for the synthesis of pyrimidothiazolo[4,5-\(b\)]quinoxaline derivatives \((42)\) via
reaction with 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (40) in acetic acid at reflux temperature (Scheme 1.16).\textsuperscript{22}

\[
\text{Me} \quad \text{CHO} \quad \text{N} \quad \text{N} \quad \text{Cl} \\
\text{Ph} \quad 40 + \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{H} \\
\text{Ph} \quad 41 \quad \xrightarrow{\text{AcOH}} \quad \text{reflux} \quad \text{H}_3\text{C} \quad \text{O} \\
\text{N} \quad \text{N} \quad 42
\]

Scheme 1.16

Condensation of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5) with malonic acid furnishes 3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)propenoic acids (43), which in the presence of Raney nickel is reduced to the corresponding propanoic acids 44. The successive conversion of both type acids into the corresponding acyl chlorides, has been performed by reaction with thionyl chloride (Scheme 1.17).\textsuperscript{23}

\[
\begin{align*}
\text{R}^1 \quad \text{CHO} & \quad \xrightarrow{\text{CH}_2(\text{CO}_2\text{H})_2} & \quad \text{R}^1 \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{H} \\
\text{Ph} & & 43 & & 45 & & 46
\end{align*}
\]

\[\text{SOCl}_2 \]

\[\text{Ni-Raney} \]

\[\text{SOCl}_2 \]

\(\text{R}^1 = \text{Ph, 4-FC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 2\text{-thienyl, 3-pyridyl, 3-coumaryl} \)

Scheme 1.17

The reaction of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile (47) and 2-(1H-benzo[d]imidazol-2-yl)acetonitrile with 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-
carbaldehydes (40) in ethanol or dioxane gives the corresponding quinazolyl-2-
propenenitrile (48) and benzimidazolyl-2-propenenitrile 50, respectively. Intramolecular
cyclization of the latter compounds in DMF in the presence of Et₃N affords pyrazolo[3,4-
b]pyrido[2,1-b]quinazoline-5-carbonitrile (49), and benzo[4,5]imidazo[1,2-a]pyrazolo[4,3-
e]pyridine-5-carbonitrile (51), respectively (Scheme 1.18).²⁴

Condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (5) with 2-cyanomethyl-4-
thiazolinone (52) in ethanol containing a few drops of piperidine yields methylene derivative
53 (Scheme 1.19).²⁵
Oximes of 4-(4-pyrazolyl)-3-buten-2-ones (54), obtained by successive reaction of (5) with acetone and hydroxylamine, upon treatment with iodine undergo an oxidative cyclization, yielding 4-(5-isoxazolyl)pyrazoles (55) (Scheme 1.20).26

Pyrazole-4-carbaldehyde (5) has been reacted with 2-hydroxyacetophenone (56) in methanol in the presence of KOH to give chalcone 57. Oxidation of 57 with hydrogen peroxide (H₂O₂) in KOH/MeOH affords 2-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-4H-chromen-4-ones (58) in high yields, these compounds display potent antifungal activity (Scheme 1.21).27,28

Condensation of substituted 2-hydroxyacetophenones (59) with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (5) produces the pyrazolylpropenones 60, which on oxidative cyclization with DMSO/CuCl₂ give the (diphenyl-1H-pyrazol-4-yl)chlorochromone (62). Condensation of 60 with 2-aminothiophenol (61) affords the benzothiazepines 63 (Scheme 1.22).29
Chalcones 64 have been synthesized by reaction of 5 with aryl methyl ketones. Condensation of 64 with barbituric acid in the presence of acetic acid affords Barbitones 65 (Scheme 1.23).
4-Pyrazolyl-4H-pyrazolopyran (70), 4-pyrazolyltetrahydrochromene-3-carbonitrile (71), and 4-pyrazolynaphthopyrans 72 and 73 have been synthesized by one-pot base-catalyzed cyclocondensation reactions of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5), malononitrile, with substituted pyrazolin-5-ones 67, dimedone 68, or naphthols 69a, 69b, respectively (Scheme 1.24). Some of these compounds show antimicrobial activity.
Pyrazolylacrylic acids 75 and pyrazolylmethylenemalonic acids 74 have been prepared by the Knoevenagel condensation of 1,3-diaryl-1H-pyrazole-4-carbaldehydes (5) with malonic acid (Scheme 1.25). Some of these compounds exhibit anti-inflammatory activity and are less active, but less toxic than phenylbutazone.\textsuperscript{32}

![Scheme 1.25](image)

Under microwave activation, 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5) react with malonic acid in the presence of a small amount of pyridine to give 3-(4-pyrazolyl)propenoic acids (76) in high yields (Scheme 1.26).\textsuperscript{33}

![Scheme 1.26](image)

A simple and rapid synthesis of 3-(1,3-diaryl-1H-pyrazol-4-yl)propanoic acids (78) using Meldrum's acid 77 from the corresponding aldehydes 5 has been reported (Scheme 1.27).\textsuperscript{34}
Knoevenagel condensation of 1,3-diphenyl-1*H*-pyrazol-4-carbaldehyde (5) has been carried out with pyrazoline (79) to give 4-pyrazolylmethylenepyrazol-5-one (80), using Borate Zirconia (B$_2$O$_3$/ZrO$_2$) solid acid catalyst in aqueous medium$^{35}$ or an ionic liquid (ethylammonium nitrate) at room temperature (Scheme 1.28).$^{36}$ In each conversion, the catalyst is successfully recovered and recycled without significant loss in yield and selectivity. On the other hand these compounds are also synthesized by traditional, microwave, and ultrasonic irradiations.$^{37-42}$

Pyrazolylmethyleneoxazolones 81 have been prepared by condensation of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (5) with acylglycine and hydrolysed to give 3-aryl-1-phenyl-4-pyrazolylpyruvic acids (82). These are converted to pyrazole-4-acetic acids 11 and pyrazole-4-acetonitriles 83 by oxidative decarboxylation using H$_2$O$_2$ and reaction with a mixture of hydroxylamine and acetic anhydride, respectively (Scheme 1.29).$^{43,44}$
Reactions of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5) with various reagents, such as benzoylglycine, and ethyl azidoacetate, afford 4-(4-pyrazolidene)-1,3-oxazol-5-ones (81), and pyrrolopyrazoles 85, respectively. Treatment of 81 with hydrazine gives the corresponding hydrazides 84 (Scheme 1.30).45,46
Biginelli coupling reaction of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (5) with ethyl acetoacetate and urea (thiourea) in the presence of FeCl₃.6H₂O,₄₇ phosphotungstic acid or a Keggin’s type heteropoly acid,₄₈,₄₉ affords 4-(3-aryl-4-pyrazolyl)-1,2,3,4-tetrahydropyrimidin-2-ones (thiones) (86) (Scheme 1.31).

1,3-Diphenyl-1H-pyrazole-4-carbaldehyde (5) has been reacted with ethyl cyanoacetate and thiourea to give the pyrimidinethione 87 (Scheme 1.32).₅₀
The Knoevenagel condensation of \(N\)-(benzothiazol-2-yl)-2-cyanoacetamide with 1,3-diphenyl-1\(H\)-pyrazole-4-carbaldehyde (5) in ethanolic sodium hydroxide (10\%) affords \(N\)-(benzothiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1\(H\)-pyrazol-4-yl)acrylamide (88), and then addition of hydrazine hydrate to the activated double bond of the compound 88 in boiling ethanol affords 5-amino-\(N\)-(benzothiazol-2-yl)-1,3-diphenyl-1\(H\),1\(H\)-3,4-bipyrazole-4-carboxamide (89). In addition, the condensation of 5-amino-\(N\)-(benzo[\(d\)]thiazol-2-yl)-3-(phenylamino)-1\(H\)-pyrazole-4-carboxamide (90) with 5 in boiling ethanol in the presence of a catalytic amount of piperidine affords the corresponding Schiff's base 91 in an excellent yield (Scheme 1.33).\(^{51}\)
Cyanoacetylhydrazine on reaction with 4-acetyl-5-methyl-2-phenylimidazole (92) gives hydrazide-hydrazone derivative 93. The reaction of 93 with pyrazole carbaldehydes 5 gives the knoevenagel adducts 94 in high yields (Scheme 1.34).52

![Scheme 1.34]

Knoevenagel condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehydes (5) with barbituric acid (95a, X = O), thiobarbituric acid (95b, X = S) in glacial AcOH affords the condensation products 84. The synthesized barbitones (96a, X = O) and thiobarbitones (96b, X = S) show antibacterial and antifungal activities (Scheme 1.35).53

![Scheme 1.35]

5-Aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3H)-furanones (98) have been prepared by condensing 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (5) with 3-arylpionic acids (97) in the presence of N,N-dimethyl(chlorosulfinyloxy)methaniminium chloride as a cyclodehydrating agent (Scheme 1.36).54
Thumar et al., synthesized a new series of 4-pyrazolyl-N-arylquinoline-2,5-dione derivatives (101) by one-pot three component cyclocondensation reaction of 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde (99), Meldrum’s acid (77) and 3-arylamino-5,5-disubstitutedcyclohex-2-enone (100) (Scheme 1.37).
1.2 REFERENCES


