Chapter-1
Importance of the heterocyclic systems containing nitrogen: a brief review on their recent synthesis
1.1 Importance of the heterocyclic systems containing nitrogen

For more than a century, heterocycles have instigated one of the largest areas of research in organic chemistry. They have contributed immensely to the development of society from biological and industrial points of view as well as to the understanding of life processes with efforts to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. Compounds possessing heterocyclic sub-units are of potential interest in biology, pharmacology, optics, electronics and material sciences. Amongst them, nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of the historical development of organic synthesis. Nitrogen-containing heterocycles are a large, diverse and important class of compounds. They are the key structural motifs of numerous materials of contemporary commercial and chemical practice, from dyes to medicines and plastics. Many are represented by biomolecules such as alkaloids, the B-vitamins, nucleobases and porphyrins, from psychoactive species to anodynes, from coenzymes to DNA and from RNA to oxygen metabolism and photosynthesis. These heterocycles usually play a decisive role in biochemical processes because the side groups of the most typical and essential constituents of living cells, the DNA and RNA, are based on nitrogen containing heterocycles. Further, some important vitamins are constructed mainly on nitrogen containing heterocyclic scaffold. In addition, most coenzymes have nitrogen heterocycles as major constituents. Numerous plant and animal hormones possess nitrogen heterocycles as their major component. The essential amino acids tryptophan and histidine are also nitrogen heterocycles which participate in protein constitution through amide linkages along with other amino acids. The fascinating ability of nitrogen based heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. Therefore, the synthesis and studies on nitrogen containing heterocycles is a work of supreme importance. A brief review on the recent trends towards the synthesis of diverse nitrogen containing heterocycles has been given below. Later, at the beginning of each chapter, a brief review of the earlier synthesis of the particular heterocyclic nucleus synthesized has been discussed.
A brief review towards the recent trends on the synthesis of nitrogen containing heterocycles

In this thesis, it is impossible to comprise all the methodologies, so I have selected some interesting examples related to my work carried out in recent years.

D. Bonne et al. developed a multicomponent synthesis of 4-imino-4H-3,1-benzoxazines by heating a solution of an aldehyde, an amine, and an isonitrile in the presence of a stoichiometric amount of ammonium chloride in toluene at 60 °C.

\[
\begin{align*}
\text{NHR}^1 + \text{R}^2-\text{CHO} & \xrightarrow{\text{NH}_4\text{Cl}} \xrightarrow{\text{Toluene, 60}^\circ\text{C}} \\
\text{NHR}^1 & \quad \text{NR}^3 \text{R}^4
\end{align*}
\]

Scheme 1.1.1.1

D. Ma and his co-workers reported the CuI/L-proline-catalyzed cross-coupling of 2-halotrifluoroacetanilides with β-keto esters and amides followed by in situ acidic hydrolysis to deliver the 2,3-disubstituted indoles. The halides bearing a strong electron withdrawing group in the 4-position can undergo in situ basic hydrolysis to provide the corresponding indoles. Polysubstituted indoles can be prepared from substituted 2-halotrifluoroacetanilides with high regioselectivity.

\[
\begin{align*}
\text{Y} & \quad \text{NHCCOF}_3 \\
\text{X} = \text{I, Br}
\end{align*}
\]

Scheme 1.1.1.2

A wide variety of substituted isoquinolin-1(2H)-ones were synthesized by Z. Zheng and H. Alper in reasonable to good yields by the palladium-catalyzed cyclization of diethyl(2-iodoaryl)malonates with imidoyl chlorides and carbon monoxide in tetrahydrofuran.
T. O. Vieira et al. described tandem palladium-catalyzed N,C-coupling/carbonylation, under carbon monoxide (10 atm) at 110 °C for the preparation of 2-carboxyindoles. The catalyst system tolerates a variety of functional groups, and the desired indoles were obtained in good isolated yields.\(^8\)

Q. Ding et al. described an efficient and practical route for the synthesis of 2-amino substituted benzothiazoles by copper(I) catalyzed tandem reaction of substituted 2-iodoanilines with isothiocyanate under mild conditions.\(^9\)

Y. M. Litvinov et al. reported a new four-component synthesis of substituted and spiro-conjugated 6-amino-2H,4H-pyran[2,3-c]pyrazol-5-carbonitriles directly from aromatic aldehydes or heterocyclic ketones, malononitrile, \(\beta\)-ketoesters and hydrazine hydrate.\(^10\)

R. C. Hodgkinson et al. reported about a Cu-diamine complex that effectively catalysed tandem C–N bond formation on 2-(2-haloalkenyl)-aryl halide substrates, to deliver

![Scheme 1.1.1.3](image-url)

![Scheme 1.1.1.4](image-url)

![Scheme 1.1.1.5](image-url)

![Scheme 1.1.1.6](image-url)
a series of $N$-functionalized indoles. Anilines, amides and carbamates all proved to be effective coupling partners under the developed conditions.\textsuperscript{11}

\[ \text{Scheme 1.1.1.7} \]

F. Lehmann et al. reported that treatment of substituted 2-nitrobenzylamines with methanolic sodium hydroxide furnished $N$-hydroxyindazoles regioselectively and in high yields. This reaction tolerates a wide range of functional groups and electronic effects.\textsuperscript{12}

\[ \text{Scheme 1.1.1.8} \]

F. Wang et al. described a simple and efficient copper catalyzed method for the synthesis of 3,4-disubstituted isoquinolin-1(2H)-one derivatives via cascade reactions of substituted 2-halobenzamides with $\beta$-keto esters under mild conditions.\textsuperscript{13}

\[ \text{Scheme 1.1.1.9} \]

Y. S. Chun et al. explored the Blaise reaction intermediate, generated in situ from Reformatsky reagent and nitrile that reacted with propiolates in a chemo- and regioselective manner to afford 2-pyridone derivatives in good to excellent yields.\textsuperscript{14}
V. L. Truong et al. reported the condensation of ortho-iodobenzaldehydes with amidine hydrochlorides under ligand-free copper catalyzed Ullmann N-arylation conditions to afford the corresponding quinazolines in good to excellent yields.\(^\text{15}\)

\[
\begin{align*}
&\begin{array}{c}
\text{R}^1\text{-CN} \\
\text{R}^2\text{CO}_2\text{Et}
\end{array} \\
\xrightarrow{\text{1. BrZnCH}_2\text{CO}_2\text{Et}} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO}_2\text{Et} \\
\text{R}^1\text{-CN} \\
\text{R}^2\text{CO}_2\text{Et}
\end{array} \\
\end{align*}
\]

Scheme 1.1.1.10

S. Maiti et al. demonstrated four component coupling reactions of 1,3-dicarbonyl compounds, amines, aromatic aldehydes, and nitroalkanes catalyzed by iron(III) salts without an inert atmosphere for the synthesis of highly substituted pyrroles using four simple and readily available building blocks via one-pot tandem reaction.\(^\text{16}\)

\[
\begin{align*}
&\begin{array}{c}
\text{R}^2\text{-CHO}
\end{array} \\
\xrightarrow{\text{FeCl}_3 (10 \text{ mol} \%) \\
\text{Reflux}} \\
\begin{array}{c}
\text{R}^1\text{-NH}_2 + \text{R}^5\text{-CH}_2\text{NO}_2
\end{array} \\
\begin{array}{c}
\text{R}^3
\end{array} + \\
\begin{array}{c}
\text{R}^4
\end{array}
\end{align*}
\]

\[\text{R}^1 \text{ and } \text{R}^2 \text{ may be alkyl or aryl} \\
\text{R}^3 = \text{Me}; \text{R}^4 = \text{Me, Ph, OMe, OEt} \\
\text{R}^5 = \text{H, Me}\]

Scheme 1.1.1.11

A highly efficient synthesis of polysubstituted oxazoles was developed by C. Wan via a copper-catalyzed tandem oxidative cyclization. The desired products can be obtained from readily available starting materials under mild conditions.\(^\text{17}\)

\[
\begin{align*}
&\begin{array}{c}
\text{Ar}\text{-NH}_2
\end{array} + \\
\begin{array}{c}
\text{R}^1\text{CO} \quad \text{R}^2\text{CO} \\
\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}, \text{I}_2, \text{TBHP}
\end{array}
\end{align*}
\]

Scheme 1.1.1.12

6
A one-pot, three-component condensation reaction of an aldehyde, 3-amino-5-methylpyrazole and ethylcyanoacetate in ethanol has been described by A. Rahmati to give 4aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitriles, in high yields, under reflux, using catalytic amount of p-toluenesulfonic acid.18

Scheme 1.1.1.14
1.2 References


