2.1 Introduction

Pyroles represent an important class of heterocyclic compounds.\(^1\) They are abundant in nature and are of great interest as subunits of natural products. In addition, substituted pyrroles often display important biological activities.\(^2\) Pyrroles are the building blocks for porphyrins\(^3\) and polymers of pyrroles have found use as conducting polymers and materials for nonlinear optics.\(^4\) They undergo a wide variety of chemical reactions including electrophilic substitution reactions, acylation and alkylation reactions at nitrogen, cycloaddition reactions and photochemical transformations. They are valuable precursors for the synthesis of a wide variety of biologically active organic molecules.\(^5\)

It is well known that chemical as well as biological properties of heterocyclic compounds depend on their substitution pattern. The development of synthetic protocols leading to new heterocyclic systems or expedient methods for known systems with control on the substitution pattern is an active area of organic chemistry research. The early impetus for the study of pyrroles came from degradative work relating to the structures of two pigments central to life processes, the blood respiratory pigment haem and chlorophyll, the green photosynthetic pigment of plants.\(^6\) Owing to their utility and biological interest numerous synthetic pathways were developed for the synthesis of pyrroles. Among different methods available for the synthesis of pyrrole ring, the
classical methods like Paal-Knorr synthesis, Knorr synthesis, Hantzsch synthesis, as well as various cycloaddition reactions are still widely used. Several variations in these methodologies are reported, that either give new pyrroles or results in improved yields of known compounds. More recently some transition metal catalyzed reactions have also come to light. The main focus of this review is on the chemical strategies used in the synthesis of substituted pyrroles giving special emphasis on recent developments in this field.

2.2 Paal-Knorr synthesis

This is the most popular method for pyrrole synthesis that utilizes the reaction between an appropriately substituted 1,4-dicarbonyl compounds\(^7\) 1 and ammonia or primary amines (Scheme 1).

![Scheme 1](image)

An alternative to the use of ammonia for the synthesis of N-unsubstituted pyrrole by this strategy employs hexamethyldisilazide with alumina.\(^8\) 2,5-Dimethoxymethoxytetrahydrofuran 4 react with aliphatic and aromatic amines, amino esters, arylsulphonamides, trimethylsilylthoxycarbonylhydrazine, or primary amides to give the corresponding N-substituted pyrroles (Scheme 2).\(^9\)

![Scheme 2](image)
Several variations in the Paal-Knorr methodology have been developed. For example, Mcl.eod et al. have reported the synthesis of 1-aminopyrroles 9 from monoprotected hydrazines like 2,2,2-trichloroethyl- and 2-(trimethylsilyl)ethyl hydrazine 7 and 1,4-dicarbonyl compounds 6 (Scheme 3). This is particularly significant as the use of hydrazine or its substituted derivatives such as tosylhydrazine, N-aminophthalimide, thiosemicarbazide, benzyl- and tert-butyl hydrazides do not condense efficiently with 1,4-diketones to form 1-aminopyrrole derivatives.

![Scheme 3](image1)

Recently Danks have demonstrated that microwaves enhance the rate of Paal-Knorr reaction. This reaction was modified by Rao for the synthesis of 2,5- and 1,2,5-trisubstituted pyrroles in a one-pot operation from 1,4-diaryl-2-butene-1,4-diones 10 through domino pathways involving the reduction of a double bond followed by reductive amination-cyclization (Scheme 4).

![Scheme 4](image2)

One drawback of the Paal-Knoor synthesis, the availability of suitable 1,4-dicarbonyl compounds, has been solved by Taylor et al. by utilizing the Kornblum-De La Mare rearrangement of 3,5-dihydro-1,2-dioxines 14 derived from 1,3-diene 13 in presence of ammonia or a primary amine(Scheme 5).
Müller et al. have reported the synthesis of 1,2,3,5-tetrasubstituted pyrroles 20 in good yields in a one pot, three step, four-component process by a coupling-isomerisation-Stetter-Paal-Knorr sequence of an electron poor (hetero)aryl halide 17, a terminal propargyl alcohol 18, an aldehyde, and a primary amine (Scheme 6).\textsuperscript{14}

\begin{center}
\textbf{Scheme 5}
\end{center}

\begin{center}
\textbf{Scheme 6}
\end{center}

\textbf{2.3 Knorr synthesis}

Synthesis of substituted pyrroles from \(\alpha\)-aminocarbonyl compounds and activated ketone is known as \textit{Knorr synthesis} (Scheme 7).
Since α-amino carbonyl compounds undergo self-condensation reaction, they are usually prepared and used in the form of their salts to be liberated for reaction by the base present in the reaction mixture. Carbonyl protected amines such as amino acetals 24 have been used, for instance in the following example with an enol ether of a β-ketoaldehyde 25 as synthon for activated carbonyl component (Scheme 8).15

A way of avoiding the difficulty of handling α-aminocarbonyl component is to prepare them in the presence of a second component, with which they are to react. The precursor of the α-aminocarbonyl component is the oxime 28 which too is derived from the other carbonyl component 29, and it is even possible to generate the oximino precursor of the amine in situ (Scheme 9).16
Bis(methylthio)nitroethene reacts with aryl or alkyl cuprates, displacing one of the methylthio groups to form 32 which reacts with amino acetal 31, as the α-aminocarbonyl synthon, to give intermediate 33 which on ring closure affords 2-substituted-3-nitropyrole 34 (Scheme 10).17

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{Et}_2\text{O} & \quad \text{Et}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{MeS}^+ & \quad \text{Bu}''^+
\end{align*}
\]

\[
\begin{align*}
\text{EtOH, reflux, 80%} & \quad \text{MeO} \quad \text{MeO} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{HCl} & \quad \text{HCl}
\end{align*}
\]

\[
\begin{align*}
\text{Bu}''^\alpha & \quad \text{Bu}''^\alpha
\end{align*}
\]

\[
\begin{align*}
\text{meOH, reflux} & \quad \text{Et}_2\text{O}, 5^\circ\text{C}
\end{align*}
\]

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

\[
\begin{align*}
\text{Bu}''^\alpha & \quad \text{Bu}''^\alpha
\end{align*}
\]

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

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

\[
\begin{align*}
\text{MeS} & \quad \text{H H}
\end{align*}
\]

\[
\begin{align*}
\text{69%} & \quad \text{69%}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 10}
\end{align*}
\]

There are examples in which two pyrrole rings are formed using a phenylhydrazone 36 as precursor of the α-aminocarbonyl component (Scheme 11).18

\[
\begin{align*}
\text{Zn} & \quad \text{AcOH}, \text{NaOAc}
\end{align*}
\]

\[
\begin{align*}
\text{115}^\circ\text{C} & \quad \text{115}^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
\text{35} & \quad \text{36}
\end{align*}
\]

\[
\begin{align*}
\text{37}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 11}
\end{align*}
\]

Methods for the assembly of the α-aminocarbonyl component include the reaction of a 2-bromoketone with sodium diformamide producing an α-formamido-ketone,19 and the reaction of a Weinreb amide of an N-protected α-amino acid with a Grignard reagent.20 The enamine 40 produced by the addition of an α-aminoester to dimethyl acetylenedicarboxylate form 3-hydroxypyrrole 41 by intramolecular ring closure (Scheme 12).21

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeOH, rt} & \quad \text{MeOH, rt}
\end{align*}
\]

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

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

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

\[
\begin{align*}
\text{Scheme 12}
\end{align*}
\]
Methyl oximinocyanooacetate 43 in a Knorr-type reductive condensation with pentane-2,4-dione 42 in hot acetic acid in the presence of zinc dust affords 3,5-dimethoxypyrrrole-2-carbonitrile 46 when acetic acid was wet, whereas, in glacial acetic acid methyl 3,5-dimethylpyrrrole-2-carboxylate 47 was formed exclusively (Scheme 13).22

Scheme 13

The regioselectivity of the Knorr synthesis using ethyl hydroxylamino acetoacetate 49 and unsymmetrical β-diketone 48 has been studied.23 The major or exclusive product has the larger alkyl substituent of the diketone incorporated as the 4-acyl substituent of the pyrrole 50 (Scheme 14).

Scheme 14

2.4 van Leusen synthesis

Addition of tosylmethyl isocyanide (TosMIC) (or benzotriazol-1-ylmethyl isocyanide–BetMIC24) to α,β-unsaturated esters or ketones with
subsequent closure onto isocyanide carbon lead to the formation of the intermediate dihydropyrrole. Proton transfer followed by elimination of toluenesulphinate generates a 3-H pyrrole which tautomerizes to the aromatic system which is unsubstituted at C-2 and C-5 (Scheme 15). \(^{25}\)

\[
\begin{align*}
\text{H}_3\text{C} & \xrightarrow{\text{TosMIC, NaH, Et}_2\text{O, rt}} \text{H}_3\text{C} \text{O} \xrightarrow{\text{H}_3\text{C} \text{N}} \text{H}_3\text{C} \text{N} \text{H} \\
51 & \quad 52
\end{align*}
\]

Scheme 15

The van Leusen’s methodology of pyrrole synthesis has been extended for the synthesis of 3-aryl pyrroles \(^{55}\) by Trudell and Parvi employing substituted cinnamates (Scheme 16). \(^{26}\) The TosMIC addition reaction with electron-rich substituents on the aryl ring did not yield the desired pyrrole, but rather gave intractable mixtures. Recently a one-step method for the synthesis of 3-aryl and 3,4-diaryl-(1H)-pyrroles has been reported by the reaction of TosMIC with arylalkenes using NaOtBu in DMSO. \(^{27}\)

\[
\begin{align*}
\text{Ar} & \xrightarrow{\text{CO}_3\text{Me, TosMIC, NaH, DMSO, Et}_2\text{O}} \text{Ar} \text{C}_2\text{Me} \xrightarrow{1) KOH, 50\% \text{MeOH}} \text{Ar} \text{N} \xrightarrow{2) \text{HO(CH}_2\text{)}_2\text{NH}_2, 3) \text{KH, CICO}_2\text{Me, THF}} \text{R}(=\text{H, CO}_3\text{Me or Boc)} \\
53 & \quad 54 \quad 55
\end{align*}
\]

Scheme 16

2.5 Barton-Zard reaction

The Barton-Zard synthesis consists of addition of the anion for isocyanoacetate to an \(\alpha, \beta\)-unsaturated nitro compound with eventual loss of nitrous acid resulting in 5-unsubstituted pyrrole-2-esters \(^{57}\) (Scheme 17). \(^{28}\)
Application of the Barton-Zard reaction and related reactions of isocyanides continue to provide important routes to 4-substituted and 3,4-disubstituted pyrrole-2-carboxylates 60 (Scheme 18). The reaction has been used to prepare pyrrolostatin and some analogues. One of the most important applications of the reaction is the synthesis of 3,4-fused pyrroles from ethyl isocyanoacetate and relatively unreactive nitro compounds such as 1-nitronaphthalene. It has been shown that the yields in such reactions can be significantly improved by using a phosphazene base instead of DBU.

Further generalizations of this approach continue to enhance its usefulness. \(\alpha,\beta\)-Unsaturated sulfones, which can be easily accessed, for example from alkenes by addition of phenylsulfenyl chloride, S-oxidation and then elimination of hydrogen chloride, react with isocyanoacetates and isocyanonitriles to give pyrrole.

Pyrroles are readily prepared from ethyl isocyanoacetate and electron-deficient alkenes, nitroalkenes and sulfonylalkenes, using a Barton-Zard type reaction in which these electron deficient alkenes act as Michael accepters. Since cycloadduct 62 derived by the cycloaddition of nitrile oxides to \(1\)-phenylsulfonyl-1,3-dienes 61, incorporates an electron deficient sulfonylalkene moiety, it appeared ideally suited for this pyrrole-forming reaction (Scheme 19).
Combining the methodologies of the van Leusen and Barton-Zard reactions, Novi et al. have prepared 2,3-disubstituted 4-ethynylpyrroles 64 and 66 from 1,4-disubstituted 2,3-dinitro-1,3-butadienes 65 (Scheme 20).\textsuperscript{35}

\begin{align*}
\text{(a) THF/TosMIC (1.1 mol. equiv.)/DBU (2 mol. equiv.)} \\
\text{(b) THF/TBICA (1.1 mol. equiv.)/DBU (2 mol. equiv.)}
\end{align*}

**Scheme 20**

### 2.6 Hantzsch synthesis

Pyrrole 70 is formed by the interaction of ammonia with a β-ketoester and alkylating the resulting β-aminocrotonate by an α-haloketone or aldehyde 67 (Scheme 21).\textsuperscript{36}

\begin{align*}
\text{Cl} \quad \text{[aq.}\text{NH}_3, n-60 ^\circ\text{C}] \\
\text{67} \quad \text{68} \quad \text{69} \quad \text{70}
\end{align*}

**Scheme 21**
2.7 1,3-Bielectrophiles in synthesis of pyrroles

The first use of glycine ethyl ester in pyrrole synthesis was as early as 1915, when Hale and Hoyt reacted it with the sodium salt of nitromalonaldehyde to obtain ethyl 4-nitropyrrrole-2-carboxylate.\textsuperscript{37} Triebis and Ohorodnik later found that 2,4-hexanodione gave the 5-ethylpyrrole isomer, when cyclized with sodium ethoxide.\textsuperscript{38} Fischer and Fink had earlier investigated the reaction of 2,4-hexanodione with glycine ethyl ester,\textsuperscript{39} in a work that clearly foreshadowed Kleinspehn’s major discovery. Modest yields of pyrrole 73, usually aryl substituted, have been reported from \( \beta \)-diketone 71 in refluxing DMF when treated with a very large excess of glycine ethyl ester hydrochloride 72 (Scheme 22).\textsuperscript{40}

\[
\begin{array}{c}
\text{R}_1 \text{C}(=\text{O})\text{R}_2 + \text{HCl} \rightarrow \text{H}_2\text{N}-\text{CO}_{2}\text{Et} \\
\text{71} \quad \text{72} \quad \text{73}
\end{array}
\]

\textbf{Scheme 22}

Several reports have appeared recently concerning the conversion of \( \beta \)-diketones or \( \beta \)-diketone analogues to pyrrole esters. Barluenga \textit{et al.} have shown that the 4-amino-1-azabuta-1,3-diene analogues of some \( \beta \)-diketones react smoothly with glycine ethyl ester hydrochloride or ethyl chloroacetate in pyridine to afford regiospecifically ethyl pyrrole-2-carboxylates.\textsuperscript{41}

A variety of methods have been employed to effect the condensation between a 1,3-diketone like 74 and a glycine ester, perhaps the simplest is condensation using triethylamine as base to produce an intermediate enaminoketone 76. This then undergoes a ring closure in a second step to afford pyrrole derivative 77 (Scheme 23).
Gupton and coworkers have recently developed iminium salt based methodology for the regiocontrolled synthesis of substituted pyrroles. A variety of 2-substituted vinamidinium salts 78 react with α-aminoesters 79 under basic conditions to afford 2,4-disubstituted pyrroles 80 in good yields (Scheme 24).42

\[
\begin{align*}
\text{74} + \text{75} & \xrightarrow{\text{Et}_3\text{N}} \text{76} + \text{EtONa, EtOH, reflux, 85%}} \\
\text{78} + \text{79} & \xrightarrow{\text{NaOC}_2\text{H}_5\text{C}_2\text{H}_5\text{OH, Heat}} \text{80}
\end{align*}
\]

Scheme 24

The reaction of 3-aryl-3-chloropropeniminium salts 81 with either glycine or sarcosine ester 82 to afford, 2-carbethoxy-5-arylpyrrole 83 in a regioselective manner (Scheme 25).43 Similar approach has been used for synthesizing 2,3-disubstituted pyrroles by the reaction of 1-arylvinamidinium salts with sarcosine ethyl ester. The corresponding reaction with glycine ethyl ester resulted in 2,5-disubstituted pyrroles.44

\[
\begin{align*}
\text{81} + \text{82} & \xrightarrow{\text{NaH, DMF, Heat}} \text{83}
\end{align*}
\]

Scheme 25

γ-Chloroiminium salts 86 produced as shown below are synthetic equivalents of 1,3-dicarbonyl compounds and can be used in the reaction with glycine ester to form the pyrrole derivatives 87 (Scheme 26).45
Scheme 26

Kenner et al. (Kenner Synthesis) has reported a method for the synthesis of pyrrole 91 from the ester of toluene-$p$-sulfonfyl glycine with $\alpha,\beta$-unsaturated ketone 88 (Scheme 27).\(^{46}\)

Scheme 27

Pyrroles derivative 95 could be prepared from 3-alkoxy acroleins 92 and N-methyl glycine ester derivative 93 as shown in Scheme 28.\(^{47}\)

Scheme 28

The reaction between N,N-dibenzylglycinate 96 and $\beta$-ketoacetals has been utilized by Wilkinson et al. for synthesizing 5-substituted ethyl pyrrole-2-
carboxylates 98. Since the requisite β-ketoacetals were prepared from β-ketoesters, this synthesis constitutes a method of transforming β-ketoesters into pyrroles (Scheme 29).48

\[
\begin{array}{cccc}
\text{CO}_2\text{Et} & \quad & \text{N(CH}_2\text{Ph})_2 & \quad \text{OH} \\
1) \text{LDA, } -78^\circ & \quad 2) \text{O} & \quad \text{R}_1 & \quad \text{H} \\
\text{96} & \quad \text{97} & \quad \text{98} & \quad \text{H}_2, \text{Pd/C, HCl}
\end{array}
\]

Scheme 29

α,β-Unsaturated ketones or their β-acetoxy carbonyl precursors condense with benzyl N-tosyl glycinate in the presence of DBU, followed by dehydration with POCl₃-pyridine and base catalyzed elimination of p-toluene sulfonic acid afford pyrrole 101 (Scheme 30).49

\[
\begin{array}{ccc}
\text{Me} & \quad \text{CH}_2\text{OAc} & \quad \text{DBU} \\
99 & \quad [\text{Me} & \quad \text{O} & \quad \text{Me}] & \quad 100 \\
1) \text{TosNHCH}_2\text{CO}_2\text{Bn} & \quad 2) \text{POCl}_3 \text{ Pyridine} & \quad 3) \text{DBU/Toluene} \\
101 & \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{Me} & \quad \text{CO}_2\text{Bn}
\end{array}
\]

Scheme 30

2.8 Other cyclization and cycloaddition reactions

An efficient method for the preparation of N-protected 5 and 2 substituted 3-bromopyrroles via acid-catalyzed cyclization of the corresponding acetylenic ketones and acetylenic acetals has been developed. The acetylenic ketones 102 and acetylenic acetals 104 were conveniently prepared from N-protected propargylamines and 3,3-diethoxyprop-1-yne respectively (Scheme 31 and Scheme 32).50

\[
\begin{array}{c}
\text{O} & \quad \text{NR}^2\text{H} & \quad \text{HBr-AcOH (33%)} \\
\text{R}_1 & \quad \text{CH}_2\text{Cl}_2, 0^\circ \text{C} & \quad \text{Br} \\
103 & \quad \text{R}_1 & \quad \text{R}_2 & \quad \text{N} & \quad \text{R}_2
\end{array}
\]

Scheme 31
The *endo-dig* cyclization of 4-tosylamino alkynes 106 in the presence of iodine generates dihydropyrroles 107. The elimination of toluenesulphinate from which produces the pyrrole 108 (Scheme 33). However, γ-ynyl-β-hydroxy-α-amino esters on exposure to toluenesulfinic or sulfonic acid in hot toluene induces *5-endo-dig* cyclization and dehydration to afford 2,5- and 2,3,5-trisubstituted pyrroles.

**Scheme 33**

Enamines 110 produced by the addition of an α-aminoester 109 to dimethyl acetyledicarboxylate form 3-hydroxypyrrroles 111 by ring closure (Scheme 34).

**Scheme 34**

Dipolar cycloaddition of alkynes to mesoionic oxido-oxazolium salts 112 followed by removal of CO₃ yields pyrrole. Azalactones generated by dehydration of N-acyl aminoacids, which are in equilibrium with mesoionic
oxido-oxazolium salts, are trapped by reaction with alkynes followed by loss of carbon dioxide to give the aromatic pyrrole 114. (Scheme 35).

\[
\begin{align*}
\text{112} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \q
5-Aminothiazolium salts can be converted into substituted 5-aminopyroles via base induced 1,3-dipolar cycloadditions with electron-deficient alkynes and alkenes. The reaction involves a 1,3-dipolar cycloaddition of the masked cyclic azomethine ylides across the olefinic or acetylenic π-bond, yielding unstable N-bridged adducts and subsequent extrusion of isothiocyanate yields the pyrroles.

Reaction of lithiated propargilic amines 122 with isothiocyanates, followed by addition of t-BuOK in t-butanol and methyl iodide has been utilized for the synthesis of N-alkyl-2-aminopyrroles 124 (Scheme 38).

\[
\begin{array}{c}
R^2\text{NCH}_2\text{C}≡\text{CH} \quad 1) \text{t-BuLi, THF} \\
R^2\text{NCH}_2\text{C}≡\text{C}≡\text{NR}^1 \quad 2) \text{R}^1\text{N}=\text{C}=\text{S} \quad \text{DMSO}
\end{array}
\]

Scheme 38

Acyclic and cyclic acyl ketene-S,N-acetals 125 undergo cuprous bromide induced cyclization with prop-2-ynyl bromide 126 to afford corresponding pyrroles 127 (Scheme 39).

\[
\begin{array}{c}
\text{R}^2\text{NH} \quad 125 \\
\text{H} \equiv \text{C}≡\text{CH}_2\text{Br} \quad 126
\end{array}
\]

Scheme 39

Cyclocondensation of trifluoromethyloxazolones 128 with electron-deficient alkenes in the presence of base affords 2-trifluoromethylpyrroles 129 (Scheme 40).
Bromination of the acetals 131 β,γ-unsaturated aldehydes also afford 3-substituted pyrrole 133 (Scheme 41).\(^1\)

\[
\begin{align*}
\text{Scheme 41} & \\
R^1 & \quad \text{1. Br}_2/\text{pentane, } -10 \degree C \\
& \quad \text{2. HCO}_2\text{H} \\
131 & \quad \text{132} \\
& \quad \text{R}^2\text{NH}_2 \\
& \quad \text{133}
\end{align*}
\]

1.3-Dienes react with palladium (II) chloride and acetic acid with the formation of 4-acetoxy-alk-2-enyl-palladium complexes which on reaction with primary amines affords N-alkylpyrroles.\(^2\)

Nam to and Farcas utilized samarium diiodide for the synthesis of pyrrole 136 by the reduction of diphenyl α-iminoketone (Scheme 42).\(^3\)

\[
\begin{align*}
\text{Scheme 42} & \\
134 & \quad \text{135} \\
& \quad \text{136}
\end{align*}
\]

2.9 Pyrroles from functionalized azides

The reaction of α-azidoketones 137 with highly stabilized Michael accepters has been utilized for the synthesis of polyfunctionalized pyrroles 139.
Here the α-azidogroup seems to act as a stable synthetic equivalent of an α-ketoketimine (Scheme 43).  

\[
\begin{align*}
\text{O} & \quad \text{R} \\
\text{137} & \quad \text{138} & \text{139}
\end{align*}
\]

Scheme 43

Reductive reaction of phenacyl azides using Kagen's reagent, samarium (II) iodide has been utilized recently by Fan and Zhang for the synthesis of 2,4-diarylpyrroles 141. The reaction normally completes within 5 minutes in high yields under mild and neutral conditions (Scheme 44).  

\[
\begin{align*}
\text{Ar} & \quad \text{N}_3 \\
\text{140} & \quad \text{Sml}_2 (2.5 \text{eq}) \\
\quad & \quad \text{THF/r} \\
\text{141}
\end{align*}
\]

Scheme 44

The azides produced by the alkylation of α-haloalkyl imines with 1-azido-2-iodoethane can be converted into 2,3-disubstituted pyrroles by successive reaction with tin (II) chloride and sodium methoxide.

Electron deficient 2H-azirine 143, derived from the vinyl azide 142, react with enamines and α-oxophosphorus ylides to give the pyrrole-2,3-dicarboxylates 144 (Scheme 45).
2.10 Recent developments

There are a number of recent reports on the synthesis of substituted pyrroles. One-pot multicomponent processes have gained considerable interest because they address the very fundamental principle of synthetic efficiency and reaction design. Another trend, with increasing frequency, in pyrrole synthesis is the transition metal catalyzed C-H bond activation induced by α-heteroatom effects. Selected examples are given here to give a glimpse of various new methods developed recently.

Low valent rhodium complexes have been utilized for the activation of α-C-H bond of isonitriles. Synthesis of pyrroles 147 was performed by cyclocondensation of isonitrile 145 with 1,3-dicarbonyl compounds 146 (Scheme 46) in the presence of rhodium catalyst. 68

\[
\text{R'NH}_2 + \text{R''C(O)R'} + \text{R'''C(O)H} \rightarrow \text{R'R''R'''}\text{NCO}_2\text{Et} \\
145 + 146 \rightarrow 147
\]

\textit{Scheme 46}

Three-component coupling of aldehyde 149, amine 148, and nitroalkanes 150 in the presence of a catalytic amount of samarium species under mild conditions afford pyrrole 151. The reaction was considered to involve the coupling of α,β-unsaturated imines, which are provided by samarium-catalyzed aldol-type condensation of imines generated from amine and aldehyde (Scheme 47). 69

\[
\text{R'NH}_2 + \text{R''C(O)R'} + \text{R'''C(NO}_2\text{H)} \rightarrow \text{R'R''R'''}\text{N_{R'}} \\
148 + 149 + 150 \rightarrow 151
\]

\textit{Scheme 47}
Recently another three-component condensation of a carbonyl compound 152, an amine 153 and nitroalkene 154 in molten tetrabutylammonium bromide as medium for the efficient synthesis of alkyl-substituted pyrroles has been reported. (Scheme 48).

\[
\begin{align*}
R'CH_2O & + R^2NH_2 + \underset{\text{n-Bu}_2\text{NBr}}{\underset{105^\circ \text{C}}{\text{1.0-1.5-h}}} \text{R}^3\text{NO}_2 \\
\text{152} & \quad \text{153} & \quad \text{154} & \quad \text{155}
\end{align*}
\]

Scheme 48

When the zwitter ion formed by the addition of isocyanide to DMAD were trapped by 156 amino pyrroles 159 were formed (Scheme 49).

\[
\begin{align*}
\text{TsN} & + \underset{\text{Benzene}}{\text{rt, Argon}} \text{R}^4 \text{NC} \\
\text{156} & \quad \text{157} & \quad \text{158} & \quad \text{159}
\end{align*}
\]

Scheme 49

A one-pot synthesis of 2,5-diarylpyrroles 161 from ketimines 160 using \(\text{TiCl}_4/\text{Et}_3\text{N}\) reagent combination has been reported by Periasamy et al. The interesting feature of this transformation is that there is no need to prepare a 1,4-diketone intermediate as in Paal-Knorr synthesis (Scheme 50).

\[
\begin{align*}
\text{Ar}^R \text{C}^R \text{CH}_3 & \quad \text{TiCl}_4/\text{Et}_3\text{N} \\
\text{160} & \quad \text{161}
\end{align*}
\]

Scheme 50
Azatitanacylclopentene complexes 163 react with carbon monoxide under atmospheric pressure to afford pyrroles 164 in good yields, providing a general method for synthesis of substituted pyrroles from an alkyne, an imine and carbon monoxide (Scheme 51). The reaction is a modified form of pyrrole synthesis reported by Buchwald and co-workers using zirconocene complexes of imines.

\[
\text{Rh}_2(OAc)_4 \text{ catalyzed reaction of the (N-tosyl)amino substituted } \alpha\text{-diazocarbonyl compounds, which in turn prepared by reaction of titanium enolate of } \beta\text{-ketodiazocarboxyl ester or ketone with an activated N-tosyl amine, leads to the efficient formation of pyrrole derivatives.}^{75}
\]

**Scheme 51**

Umpolung reaction of 2-acetoxy aldehyde dimethylhydrazone 165 with silyl enol ethers 166 in the presence of titanium tetrachloride and reductive N-N bond cleavage of the resulting 1-(dimethylamino)-1H-pyrroles 167 provides an efficient and flexible method for the regioselective synthesis of alkyl and aryl-substituted 1H-pyrroles 168 (Scheme 52).^{76}

**Scheme 52**

1a) TiCl4, CH2Cl2, -78 °C, 15 min. (b) CH2Cl2, -78 °C to -20 °C, 3h (c) 5% aq Na2CO3, (d) p-CH3C6H4SO3H, toluene, reflux, (e) Na/NH3, rt, 8-10 bar, 3h.
N-Arylpyrroles 172 are synthesized by the reaction of unfunctionalized dienes 170 with nitroarenes 169 and carbon monoxide, catalyzed by palladium-phenanthroline complexes. Initially the hetero-Diels-Alder adduct 171 (oxazine) was formed at 100 °C which eliminates a molecule of water on heating at 200°C leading to N-arylpyrroles (Scheme 53)⁷⁷. With 1,4-disubstituted-1,3-dienes only trace amount of oxazine was detected.

\[
\begin{align*}
\text{ArNO}_2 + \begin{array}{c} \text{Pd(Phen)}_2(BF)_2 \end{array} & \xrightarrow{60-120 \degree C, 5-30 \text{ bar}} \text{O} \rightarrow \text{N-Ar} - \text{H}_2\text{O} \\
\text{169} & \text{170} & \text{171} & \text{172}
\end{align*}
\]

Scheme 53

Palladium catalyzed cyclization of amino allenes 173 to arylated pyrroles 174 was reported by Dieter and Yu (Scheme 54).⁷⁸

\[
\begin{align*}
\text{R}^1 \begin{array}{c} \text{Pd(PPh}_3)_4 \end{array} & \xrightarrow{\text{DMF, K}_2\text{CO}_3, 70 \degree C} \text{P} \rightarrow \text{Ar} \\
\text{173} & \text{174}
\end{align*}
\]

Scheme 54

Deprotonation of silyl-protected 2-\textit{E}-buten-1-amine 175 with 3 equiv. of \textit{n}-butyllithium in benzene in the presence of 1 equiv. of THF at 60 °C to form the dilithio species 176, followed by addition of various carbonyl compounds at 0 °C, affords 2,3-disubstituted pyrroles 177 in good yields (Scheme 55).⁷⁹

\[
\begin{align*}
\text{175} & \xrightarrow{3 \text{ eq. } \textit{n}} \text{butyl} \text{ lithium, 1 eq } \text{THF, benzene, 60 \degree C} \rightarrow \text{N-Si} \rightarrow \begin{array}{c} (1) \text{RCOX, O } \degree C \end{array} \rightarrow \text{LiL} \\
\text{175} & \text{176} & \text{177}
\end{align*}
\]

Scheme 55
Pyrrole synthesis by the reaction of chromium carbene complexes and alkynes were reported in 1990 and Danks have modified that method by reacting simple chromium carbene complexes 178 with 1-azadienes 179 (Scheme 56).

\[
\begin{align*}
\text{(CO)}_5\text{Cr} & \equiv \text{Et} + \text{Ph}-\text{C} \equiv \text{NR} \\
178 & \quad \text{Heat} \\
& \quad \text{C}_7\text{H}_8, 18 \text{ h} \\
\text{Ph} & \quad \text{Ph} \\
& \quad \text{N} \\
179 & \quad 180
\end{align*}
\]

Scheme 56

N-Substituted pyroles 182 are obtained when α,β-unsaturated imines 181 are combined with NbCl₃(DME) and an ester or N,N-dimethylformamide in tetrahydrofuran (Scheme 57).

\[
\begin{align*}
\text{R}^1 & \text{N} - \text{R}^2 \\
& \quad \text{R}^3 \text{C(O)Y} \\
& \quad \text{NbCl}_3(\text{DME}) \\
& \quad \text{THF} \\
181 & \quad \text{R}^4 \text{C(O)Y} \\
& \quad \text{R}^5 \text{C(O)Y} \\
& \quad \text{R}^6 \text{C(O)Y} \\
181 & \quad \text{R}^4 \text{C(O)Y} \\
& \quad \text{R}^5 \text{C(O)Y} \\
182
\end{align*}
\]

Scheme 57

1,2,3,5-Tetrasubstituted pyrrole derivatives 186 were synthesized from 2-(2-bromoallyl)-1,3-dicarbonyl compounds 184 via the intermediate formation of enamine 185 (Scheme 58).

\[
\begin{align*}
\text{R}^1 \text{C(O)} - \text{R}^2 \\
& \quad \text{Br} - \text{C} \equiv \text{C} \equiv \text{Br} \\
& \quad \text{K}_2\text{CO}_3 \\
183 & \quad \text{R}^1 \text{C(O)} - \text{R}^2 \\
& \quad \text{Br} - \text{C} \equiv \text{C} \equiv \text{Br} \\
184
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 \text{NH}_2, \text{benzene} & \quad \text{p-TsOH, reflux} \\
& \quad \text{R}^1 \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
185 & \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
& \quad \text{NHR}^3 \\
186
\end{align*}
\]

Scheme 58
N-allylbenzotriazole 187 has been utilized by Katrizky et al. for the synthesis of 1,2-diaryl or heteroaryl pyrroles 189 via intramolecular cyclization in the presence of Pd (II) catalyst (Scheme 59).

\[
\text{BuLi} \quad \text{X} \quad (1) \quad \text{Ar}^1 \quad \text{CH} = \text{N} \quad \text{Ar}^2 \\
(2) \quad \text{Ar}^1 \quad \text{CH} = \text{N} \quad \text{Ar}^2
\]

**Scheme 59**

In conclusion, development of novel methods for the synthesis of pyrrole is still an active area in synthetic organic chemistry. Appropriately substituted pyrroles are used in the synthesis of a variety of pyrrole containing natural products.

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