Chapter 1

MULTI-COMPONENT REACTIONS FOR THE SYNTHESIS OF DIVERSE HETEROCYCLIC SCAFFOLDS
1.1. Introduction

Multi-component reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product (Figure 1).\(^1\) In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.\(^2\)

![Figure 1. A divergent 1-component reaction and convergent 2- and multi-component reactions](image)

In the drug discovery process, MCR offers many advantages over traditional approaches. With only a limited number of chemists and technicians, more scaffold synthesis programs can be achieved within a shorter time. With one-pot reactions, each synthesis procedure (weighing of reagents, addition of reagents, reaction/time control) and work-up procedure (quenching, extraction, distillation, chromatography, weighing, and analysis) needs to be performed only once, in contrast to multi-step synthesis. MCRs are compatible with a solution phase approach, thus enabling a simple monitoring, and they are easily amenable to automation. Moreover, each scaffold is expandable from a low number of compounds (scouting library) to a larger library. Thus, “hit-to-lead” transitions are normally accomplished easily and promptly. Certain physicochemical properties can be built into a library, e.g. lipophilicity and aqueous solubility, molecular weight, numbers of hydrogen donors and acceptors, and the number of rotatable bonds, as well as the polar surface area. Finally, scale-up is often possible from a preclinical lab-scale (mg, gram) to clinical exploratory amounts (kg) using the same type of chemistry.\(^2\) Drug molecules derived from MCR are very cost effective which, is the need of the hour.

The usefulness of a reaction is correlated to several factors: the number of bonds which are formed in one sequence, which Tietze\(^6\) has referred to as the bond-forming efficiency (BFE, or bond-forming economy); moreover, to the increase in structural complexity (structure economy); and finally, to its suitability for general application. Multi-component reactions have attracted
considerable interest owing to their exceptional synthetic efficiency. The BFE is an important measure to determine the quality of a multi-component reaction (Figure 2).

Figure 2. Two example of isocynide based MCRs with high bond forming efficacy (BFE). The 3-CR of shown above of a β-aminothiocarboxylic acid, an aldehyde and a 2,2-dimethylamino-1-isocynano alkene affords a complex molecule under mild conditions, with two heterocycles in the product that are not present in the starting materials: a β-lactam and a thiazole. During this one-pot transformation 1 C-C, 2 C-S and 2 N-C bonds are formed. Below: In the second isocynide based MCR, the isocyanoacetamide reacts four times in a highly ordered manner creating three heterocyclic rings with the concomitant formation of five chemical bonds (3 C-C bonds, 2 C-N bonds) and a minimal loss of molecular weight.

Unlike the usual stepwise formation of individual bonds in the target molecule, the defining attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents. It is obvious that adopting such strategies would allow the minimization of both waste production and the expenditure of human labor. The products are formed simply by mixing the corresponding set of starting materials. Since the structures of the products carry portions of all the reactants employed, MCRs that have a high attendant BFE assure a marked increase in molecular complexity and diversity. A wide variation among these starting materials opens up versatile opportunities for the synthesis of compound libraries. The generalization to as many available starting materials as possible is an indispensable characteristic for the most general application. Multi-component reactions thus address the requirements for efficient high-throughput synthesis of compounds in a cost- and time-effective manner. Reactions that build up carbon-carbon, carbon-nitrogen and other carbon-heteroatom bonds and at the same time introduce heteroatom-
containing functionality into the structural framework are especially attractive for the rapid construction of organic molecules.

Briefly speaking the application of MCRs in organic synthesis is tremendously increasing because –

1. They offer a wealth of products, while requiring only a minimum of effort.
2. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one pot.
3. The structure of the reaction product is easily diversified by systematic variation of each input.
4. The starting materials are either commercially available or easily prepared.
5. The number of theoretically accessible compounds is extremely large.

By nature, MCRs are by no means restricted to a particular application, but rather they can be used advantageously in any area of modern chemistry-based technology. Recent applications of MCRs unrelated to drugs include EPR-spin labeling, biocompatible materials, e.g. for artificial eye lenses, polymers with novel properties, chiral phases for HPLC, natural product synthesis, peptide-nucleic acids and agrochemicals. However in present review, we are focusing its application in heterocyclic synthesis which is also very important because majority of drugs and pharmaceutically important compounds belongs to heterocycles.

The application of MCRs in the synthesis of heterocycles is known since prebiotic era. Nature, utilizes this for the synthesis of many important biomolecules such as adenine, one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN, a plentiful component of prebiotic atmosphere, in a multi-component reaction catalyzed by NH₃ (Scheme 1). In a similar way other nucleic bases have been generated via multi-component reactions involving HCN and H₂O.

\[
\begin{align*}
5 \text{HCN} & \rightarrow \\
\text{NH}_2 & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{H}
\end{align*}
\]

Scheme 1. Prebiotic synthesis of adenine

A growing number of products, including many heterocycles, can be prepared by MCRs just by mixing three or more educts, and in many cases practically quantitative yields of pure products can be obtained. A three-component reaction (α-aminoalkylations of nucleophiles) began in the middle of the 19th century and Hantzsch introduced the syntheses of heterocycles (1,4-
dihydropyridines and pyrroles) by MCRs in the 1880s. Another significant contribution made by Biginelli (1891) who synthesized 3,4-dihydropyrimidinones via a three-component coupling of an aldehyde, urea and \( \beta \)-keto esters. Robinson (1917) was first to synthesize the naturally occurring alkaloid tropinone (an N-heterocycle) using Mannich reaction. The MCRs of the isocyanides (Ugi and Passerini reaction and related MCRs) are also very important in the synthesis of diverse heterocyclic scaffolds. Many natural products have been synthesized by MCRs. Today a large number of MCRs are known and many of them have been successfully applied to the synthesis of heterocycles (Figure 3).

**Figure 3. Examples of heterocyclic scaffolds targeted using MCRs**
Although MCRs are important tools to synthesize almost all class of heterocyclic compounds, there is no comprehensive review on MCR derived heterocycles. Most important reviews on MCRs are isocyanide based MCRs, MCR derived synthesis of natural products and synthesis of heterocycles by transition metal mediated MCRs. We are presenting here the MCR derived synthesis of heterocyclic scaffolds of all classes. The classification has been made according to the size of heterocyclic ring (3 membered, 4 membered, 5 membered, 6 membered and large heterocycles). Further classification has been made according to the number and type of heteroatom in the ring.

1.2. Three membered heterocyclic compounds

1.2.1. Aziridines

The smallest possible saturated aza heterocycle, aziridine, is well-known to organic chemists for its tremendous potential in organic synthesis and medicinal chemistry. Although aziridines are highly reactive, this skeleton occurs in several natural products and many synthetic compounds of biological interest also contain the aziridine framework in their structures (Figure 4).

![Figure 4. Aziridine containing bioactive compounds](image)

Aziridines are the precursors for the synthesis of various types of nitrogen-containing compounds, which are biologically important, such as β-lactams, azinomycins, tetrahydropyridines, indolizidine and pyrrolizidine alkaloids, allylic amines, and amino acids amino alcohols etc.

A literature survey reveals an extensive investigation of the synthesis and chemistry of aziridines since the first synthesis by Gabriel in 1888. Although numerous methods have been reported for the synthesis of substituted aziridines, carbene transfer to the imine double bond (C=N) is one of the most efficient method. However, when imines derived from aliphatic aldehydes were used, the carbene transfer was unsatisfactory and aziridines were obtained in low yields. Another drawback was the considerable amount of the side products obtained during the course of reaction. In order to rule out these difficulties in aziridine synthesis many transition metals catalyzed MCRs were developed.
Ishii et al.\textsuperscript{20} reported a three-component coupling reactions of aliphatic aldehydes, aliphatic amines and ethyl diazoacetate leading to the corresponding aziridine derivatives by the use of [Ir(cod)Cl]\textsubscript{2} as a catalyst under mild conditions (Scheme 2). The procedure is equally applicable to both the aromatic as well as aliphatic aldehyde. Aziridine derivatives are prepared in high stereoselectivity (cis:trans >95:5). Instead of THF, ethanol was also found suitable solvent for the reaction. It is also noteworthy that the yields are little affected when reactions are carried out in the presence of water.

\begin{equation}
\text{Cat} \text{[Ir(cod)Cl]}_2 \rightarrow \begin{array}{c}
R^1\text{CHO} + R^2\text{NH}_2 + N_2\text{CHCOOEt} \\
\text{THF, -10°C, 3h}
\end{array}
\end{equation}

\textbf{Scheme 2.}

The one pot coupling of aldehyde, amine and ethyl diazoacetate were further investigated and improved by Yadav et al.\textsuperscript{21} They found Bi(OTf)_3-\text{[Bmim]}PF_6 as a reusable catalyst system for the preparation of cis aziridines. LiClO_4 was also found equally effective for cis azidiation of imines. With LiClO_4 stereoselectivity (cis/trans) was found 82 to 100%. No side products such as enamines or diethyl maleate were obtained.

Budynina et al.\textsuperscript{22} reported a three-component, one-pot reactions of tetranitro- and bromotrinitromethanes, alkoxyacetylenes and diazomethane or bicyclobutylidene, yielding gem-dinitroaziridines via sequential electrophile transfer followed by [3+2]-cycloaddition. Electron rich alkynes, such as ethoxyacetylene and 1-ethoxy-1-butyne, reacted as dipolarophiles with dinitronitronates to provide unstable 3,3-dinitro-2,3-dihydroisoxazoles, which then underwent a spontaneous rearrangement (a 1,3-sigmatropic rearrangement) to afford gem-dinitroaziridines (Scheme 3). The reaction generally occurs with high regioselectivity and gem-dinitroaziridines are exclusively obtained.

\begin{equation}
\begin{array}{c}
\text{Scheme 3.}
\end{array}
\end{equation}
1.3. Four membered heterocycles

1.3.1. \(\beta\)-Lactams

The most important heterocycles with four-membered rings are the antibiotics (penicillins and cephalosporins series), both of which contain the azetidinone ring (Figure 5).\(^{23}\) The chemistry of azetidiones, or \(\beta\)-lactams, as they are also called, was explored thoroughly during the intensive research into penicillin structure and synthesis that took place during World War II. However, a practical synthesis of penicillin was not achieved, until 1959.

![Figure 5.](image)

Cephalosporin

Benzylpenicillin

The development of efficient routes to synthesize \(\beta\)-lactams is an area of significant research interest.\(^{24}\) This has been driven, largely due the importance of these molecules as constituents of antibiotics, ranging from penicillin-based substrates to a number of more recently developed compounds (e.g., penems, cephems, monobactams, carbapenems, and trinems).\(^{25}\) \(\beta\)-Lactams have also been demonstrated to be important synthons in organic synthesis\(^{26}\) and to be monomers in the generation of polyamides (e.g., poly(\(\beta\)-peptides)).\(^{27}\) The classical and improved methods for \(\beta\)-lactam synthesis were recently reviewed.\(^{28}\)

1.3.1.1. \(\beta\)-Lactams via 1, 3-dipolar cycloaddition

The reaction of aldehydes with alkyl/aryl-hydroxylamine hydrochlorides generates nitrones which undergo 1,3-dipolar cycloaddition with olefins to yield isoxazolidines. When the olefin contains a cyclopropane ring at least on its one terminal, the resulting isoxazolidines undergoes ethylene elimination with simultaneous formation of \(\beta\)-lactams.

Based on this unprecedented fragmentation of 5-spirocyclopropanated isoxazolidines to \(\beta\)-lactams, Zanobini et al have developed a one-pot three-component reaction for the direct conversion of certain alkyl/aryl-hydroxylamine hydrochlorides, aldehyde and bicyclopropyldiene to furnish 3-spirocyclopropanated 2-azetidinones (Scheme 4).\(^{29}\) The reaction has been carried out in intramolecular way to yield many biologically important \(\beta\)-lactam compounds.\(^{30}\)
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

Scheme 4.
Li and Zhao\textsuperscript{31} reported a three-component reaction of N-substituted hydroxylamines, aldehydes, and phenylacetylene catalyzed by CuCl/2,2'-bipyridine in the presence of NaOAc under neat conditions affording to the corresponding \(\beta\)-lactams in good to excellent yields (Scheme 5).

\[
\begin{align*}
\text{RCHO} + \text{MeNHOH.HCl} &\overset{5 \text{ mol\% CuCl, 5 mol\% 2,2'-bipyridine}}{\longrightarrow} \text{Ph} &\overset{30 \text{ mol\% NaOAc, 1 eq. KHCO}_3}{\longrightarrow} &\text{R}\text{N}\text{Me} \\
&&70^\circ\text{C, neat}
\end{align*}
\]

\textbf{Scheme 5.}
N-benzylhydroxylamine is also very effective for this three-component \(\beta\)-lactam formation. Since the benzyl group on the \(\beta\)-lactam nitrogen atom can be removed readily by standard hydrogenolysis, the three-component reaction provides a very effective method for the synthesis of \(\beta\)-lactams that do not have any substituent on the nitrogen atom.

\textbf{1.3.1.2. \(\beta\)-Lactams via transition metal mediated CO insertion}
Transition-metal catalysis serves as a useful tool, where the diverse reactivity of metal complexes can be used to mediate the coupling of traditionally unreactive precursors. This approach not only can provide a straightforward overall synthesis but also is amenable to structural diversification. Dhawan et al\textsuperscript{32} reported the application of this approach to the construction of the amino acid-based \(\beta\)-lactam core, the functional structure of many biologically relevant \(\beta\)-lactams. This was done by considering the structure to be comprised of four units, two imines, acid chloride, and carbon monoxide (scheme 6), brought together in a palladium-catalyzed reaction. Considering the nature of the building blocks, this provides a modular method to construct a \(\beta\)-lactam, where five separate substituents can be independently varied in a single-pot reaction.
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

This multi-component process is directly amenable to structural diversification. The formation \( \beta \)-lactams proceeds smoothly with a number of imines and acid chlorides, all generating product in good yields and as a trans isomer. Both aryl and alkyl acid chlorides can be employed. However, the yields of \( \beta \)-lactams are lower with electron-withdrawing substituents on the imines. Palladium-catalyzed carbonylation of the allyl phosphate in the presence of imines, under CO pressure is highly stereoselective reaction since the formation of the trans- or the cis- \( \beta \)-lactam depends on the imine used for the coupling. An imine conjugated with a carbonyl group gives the cis-\( \beta \)-lactam, whereas the unconjugated imine gives the trans isomer (Scheme 7). But when allyl bromide,\(^{33}\) allylacetate,\(^{34}\) allyl phenyl ether,\(^{35}\) allyl carbonate\(^{36}\) or allylsulfone\(^{37}\) were used under similar reaction conditions no reaction products, or just traces of \( \beta \)-lactams, were formed.

Troisi et al.\(^{38}\) found that simple allyl halides of different structures, under CO pressure, in the presence of \( \text{Et}_3\text{N} \), a catalytic amount of \( \text{Pd(OAc)}_2 \), and triphenylphosphane as ligand, undergo a [2+2] cycloaddition reaction with various imines. The reaction is highly regio and stereoselective. \( \beta \)-Lactams are formed in good yields and with trans diastereoselectivity (Scheme 8).
1.3.1.3. β-Lactams via Ugi reaction

Aliphatic β-amino acids have been tremendously used in the Ugi reaction, resulting in a monocyclic β-lactam library. Gedey et al reported a parallel liquid-phase synthesis of β-lactams, utilizing cyclic β-amino acids in an Ugi four-center three-component reaction (U-4C-3CR). Recently, β -lactam libraries were synthesized using the Ugi four-centre three-component reaction (U-4C-3CR), in aqueous medium. The β-lactam libraries are generated using aliphatic or aromatic aldehydes, cyclic β-amino acids and cyclohexyl or tert-butyl isocyanide (Scheme 9).

The concentration is a determining factor in this reaction. Precipitation occurs when less water-soluble β-amino acids and an appropriate amount of water were used. In this way, the reactions are complete in 1 day at room temperature, as compared with a 3 days reaction in methanol. It should be noted that the relatively poor solubility of the different aldehydes in aqueous medium reduce their applicability. The diastereomeric ratio of the product ranged from 60 : 40 to 100 : 0. When the β -amino acid component contained a norbornane or norbornene skeleton, the quantitatively diastereoselective reactions were observed. Comparison of the diastereomeric ratios obtained in the aqueous phase or in an organic solvent did not reveal appreciable differences. However, the yields were slightly better in water than in organic media.

Scheme 9.

Alicyclic β-lactams have been synthesized via the Ugi reaction on a solid support. Via the Ugi 4-centre 3-component reaction (U-4C-3CR), bicyclic cis-2-azetidinone derivatives were synthetised from cyclic β-amino acids on Super Acid Sensitive Resin (Sasrin). 2, 3 or 4-Formylbenzoic acid was immobilised on the resin through its carboxy function. The U-4C-3CR was also carried out in solution, making use of scavenger resins for purification.

Five sets of 27-membered combinatorial libraries of alicyclic β -lactams were prepared via liquid-phase Ugi 4-center 3-component reactions (U-4C-3CR) utilizing 3 different cis β-amino acids, 3 different isonitriles and 5x3 sets of aldehydes. Through combinations of the building blocks of one of these libraries, all of the possible sublibraries were also generated.

A multi-component reaction of β-aminothiocarboxylic acids, aldehydes, and 3-dimethylamino-2-isocyanoacrylate is described by Domling et al. During the course of this reaction two heterocyclic moieties, a thiazole and a β-lactam ring, are formed simultaneously and under mild conditions.
conditions (Scheme 10). The increase in molecular complexity here is dramatic as 2 C-N, 2 C-S and 1 C-C bonds are formed in a one-pot, multi-component reaction.

\[
\begin{align*}
\text{H}_2\text{N}-&\text{CO}_2\text{H} + \text{OHC} + \text{MeOOC-N} \\
\rightarrow &\text{MeOOC} \\
\end{align*}
\]

Scheme 10.

1.3.2. Aza-β-Lactams

Naskar et al.\textsuperscript{44} reported the synthesis of aza-β-lactams via tandem Petasis–Ugi multi-component condensation and 1,3-diisopropylcarbodiimide (DIC) condensation reaction. Compound 1 were generated via a Petasis three-component condensation reaction followed by Boc deprotection (Scheme 11). Upon evaporation of the crude reaction mixture, the resulting hydrazine salts were treated directly with one equivalent each of aldehyde and an isocyanide in aqueous methanol. Stirring for 24 h at room temperature, provided 2 in 23-79% yields after purification. The reaction does not proceed well without water.

\[
\begin{align*}
\text{R}^1\text{H} &\quad \text{BocHN} \\
\text{HCOOH} &\quad \text{(1) Petasis} \\
\text{R}^2\text{B(OH)}_2 &\quad \text{(2) de Boc} \\
\end{align*}
\]

Scheme 11.
1.4. Five membered heterocycles

Five membered heterocyclic compounds are very rich in nature. Five member heterocyclic rings generally contain 1N, 2N, 3N, 1O, 2O, 1S, 1N + 1O, 1N + 1S, 1N + 2O, etc as heteroatoms.

1.4.1. Five membered heterocycles containing one heteroatom

1.4.1.1. Pyrrolidine derivatives

1.4.1.1.1 Pyrrolidines via 1, 3-Dipolar cycloaddition

Pyrrolidine derivatives are generally synthesized by 1,3-dipolar cycloaddition of azomethine ylides with alkenes. Azomethine ylides are planar molecules composed of one nitrogen atom and two terminal \( sp^2 \) carbons, and have four \( \pi \) electrons spread over the three-atom C-N-C unit (Figure 6). The 1, 3-dipolar cycloaddition of azomethine ylides with alkene or alkyne is a very effective method for the construction of pyrrolidine- and pyrrole-rings in the synthesis of pyrrolidine and pyrrole-containing molecules. These molecules are very important pharmaceuticals, natural alkaloids, organic catalysts, and building blocks in organic synthesis.\(^{45} \)

As with other cycloaddition reactions, it is generally accepted that the 1,3-dipolar cycloaddition of azomethine ylides follows a concerted pathway and proceeds according to the Woodward-Hoffman rules. However, a stepwise pathway can not be ruled out.\(^{46} \)

![Figure 6.](image)

Reaction of secondary amines like 2-picolyamine and aldehydes yields imines which readily tautomerized to azomethine ylides (Figure 7). The azomethine ylide has been made to undergo a \([3+2]\) cycloaddition reaction with a number of dipolarophiles.\(^{47} \)

![Figure 7.](image)

The reaction of \( \alpha \)-amino acid esters (acyclic or cyclic) with aldehydes or activated ketones generates azomethine ylids. The reaction has been applied for the synthesis of polysubstituted
pyrrolidines\textsuperscript{50} spirooxindolo pyrrolidines, spirooxindolo thiapyrrolizidines\textsuperscript{51} and prolines (Scheme 12).\textsuperscript{52} The cycloaddition are generally highly regioselective.

\[ \text{R}^1\text{O} \text{O} \xrightarrow{\text{CH}_2\text{O}} \text{H}_2\text{O} \quad \left[ \begin{array}{c} \text{R}^1\text{O} \text{O} \\ \text{X} \end{array} \right] \xrightarrow{\text{X}} \text{R}^1\text{O} \text{O} \text{X} \]

\[ \text{X} = \text{CN} \quad \text{COOEt} \]

\[ \text{MgBr}_2 \cdot \text{OEt}_2 (10 \text{ mol\%}) \text{THF, Reflux} \]

\[ \text{The azomethine ylides are generated from the reaction of } \alpha\text{-amino acids and aldehydes or activated ketones. The azomethine ylide has been coupled with a number of conjugated olefins to yield pyrrolidines (Scheme 13).}\textsuperscript{53} \text{The azomethine ylide generated by the reaction of amino acids and aldehydes has also been trapped in fullerenes.}\textsuperscript{54} \]

\[ \text{H}_2\text{COOH} + \text{HCHO} + \xrightarrow{\text{Toluene Reflux}} \]

\[ \text{Ar} \]

\[ \text{Scheme 12.} \]

\[ \text{The reaction of } \alpha\text{-diazo esters with imines generates transient azomethine ylids. The ylide thus generated is then reacted with various dienophiles to generate pyrrolidine derivatives in a highly convergent manner.}\textsuperscript{55} \text{The reaction is catalyzed by transition metal salts (Scheme 14).} \]
Galliford et al reported a catalytic, multi-component approach employing dipolarophile derived from isatin. They synthesized Spiropyrrolidinyloxindole compounds in moderate to excellent yield via a highly diastereoselective Cu(I)-catalysed three-component assembly reaction of an imine, diazo-compound and substituted olefin dipolarophile (Scheme 15).

Xu et al have synthesized chiral multi-functionalized pyrrolines by a ruthenium porphyrin catalyzed three-component coupling reaction (Scheme 16). In a one-pot reaction, ruthenium porphyrins catalyzed in situ generation of chiral azomethine ylides from chiral diazo esters and imines. Asymmetric 1,3-dipolar cycloaddition reactions of the chiral azomethine ylides with dipolarophiles afforded the corresponding pyrrolines in good yields and high diastereoselectivity (up to 92% de).

Pyrrolidines are synthesized via the reaction of the aldimines, generated in situ by the reaction of primary amines or anilines and aldehydes, with various 1,1-cyclopropanediesters in the presence of Lewis acids like Yb(OTf)₃, MgI₂ or Et₂Al₂ (Scheme 17).
Chapter I

Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

1.4.1.3. Pyrrolidines via isocyanide based MCRs

Isocyanides base multi-component reactions are very important in the synthesis of heterocycles. Ugi reaction is a well known isocyanide based reaction. It has been successfully applied in the synthesis of pyrrolidines. A three-component coupling reaction of arynes, isocyanides and N-tosylaldimines has been developed to offer modest to high yields of diverse 2-iminoisoindolines in one step (Scheme 18). Intermediacy of arynes in the coupling has been verified by the reaction of unsymmetrical arynes.\(^{61}\)

Scheme 18.

Nair et al reported an efficient multi-component reaction of N-tosylimines, DMAD, and isocyanides for the synthesis of 2-aminopyrrole systems (Scheme 19).\(^{62}\)

Scheme 19.

Zhu et al reported a sequential two-step reaction involving an Ugi four-component reaction (Ugi-4CR) and a palladium-catalyzed intramolecular amidation of aryl iodide for rapid access to functionalized oxindole.\(^{63}\) Microwave heating was used to accelerate and to improve the efficiency of the intramolecular Buchwald-Hartwig reaction (Scheme 20).
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

2009

(a) MeOH, rt
(b) Pd(dba)$_2$ (5 mol%)
ligand, K$_2$CO$_3$ (2 equiv)

\[ \text{R}^1\text{NH}_2 + \text{R}^2\text{CHO} + \text{R}^3\text{COH} \rightarrow \text{R}^2\text{R}^4\text{NC} \]

\[ \text{H}_2\text{N} - \text{R}\text{R}^1 \text{NH}_2 \]

\[ \text{R}^2\text{R}^4\text{NC} \]

\[ \text{R}^3\text{COH} \]

\[ \text{PhMe}/\text{MeCN} = 3/1 \]

\[ \text{Pd(dba)}_2 \]

\[ \text{H}_2\text{N} - \text{R}\text{R}^1 \text{NH}_2 \]

\[ \text{R}^2\text{R}^4\text{NC} \]

\[ \text{R}^3\text{COH} \]

\[ \text{PhMe}/\text{MeCN} = 3/1 \]

**Scheme 20.**

The zwitter ion generated from the reaction of dimethyl acetylenedicarboxylate and isocyanides reacts with various quinoneimides to afford the corresponding spiroiminolactams in good yields (Scheme 21).

\[ \text{NSO}_2\text{Ph} \]

\[ \text{COOMe} \]

\[ \text{PhO}_2\text{SN} \]

\[ \text{COOMe} \]

\[ \text{Benzene, 80°C} \]

\[ 4\text{h, 64%} \]

**Scheme 21.**

Yamamoto et al reported a palladium-catalyzed three-component coupling reaction of aryl isocyanides, allyl methyl carbonate, and trimethylsilyl azide in the presence of Pd$_2$(dba)$_3$.CHCl$_3$ (2.5 mol %) and dppe (1,2-bis(diphenylphosphino)ethane) (10 mol %). This palladium-catalyzed reaction has been utilized for the synthesis of N-cyanoindoles (Scheme 22).

\[ \text{R}^2\text{COOMe} \]

\[ \text{TMSN$_3$} \]

\[ 2.5\text{ mol% Pd(dba)$_3$ . CHCl$_3$} \]

\[ 10\text{ mol% (2-furyl)$_3$P} \]

\[ \text{Octane, 100°C} \]

**Scheme 22.**

1.4.1.4. Pyrrolidines via miscellaneous MCRs

An efficient one-pot synthesis of the pyrrolidines based on a multi-component domino reaction between imines and 3-nitro-1-propanol methanesulfonate has been developed (Scheme 23).

\[ \text{RCHO} + \text{R'}\text{NH}_2 \]

\[ \text{MgSO}_4 \]

\[ \text{RCH=NR'} \]

\[ \text{DABCO (Cat)} \]

\[ \text{or Basic Al$_2$O$_3$} \]

**Scheme 23.**
Palacios et al have reported a simple and efficient synthesis of 3-amino-1,5-dihydro-2H-pyrrol-2-
ones.\(^\text{67}\) These cyclic dehydro-amino acid derivatives with a stereogenic center at the 5-position
were obtained by the addition of two equivalents of amine to \(\beta,\gamma\)-unsaturated keto esters. These
cyclic enamines were obtained by the three-component reaction of ethyl pyruvate, amines and
aldehydes (Scheme 24).

\[
\text{COOEt} + \text{H}_2\text{NR}^2 + \text{HSO}_4^{\text{(cat)}} \rightarrow \text{R}_1^2 \text{RN}^1 \text{N}^\text{H}^+_1 \text{EtOOC} = \text{H}^+_1
\]

\[
\text{R}_2^2 \text{HN} + \text{R}^2 \text{HNN} \rightarrow \text{R}_1^2 \text{R}^1 \text{R}^2 \text{HN} \text{N}^\text{H}^+_1 \text{EtOOC} = \text{H}^+_1
\]

Scheme 24.

Azoulay et al reported a three-component synthesis of stereo-defined 4-benzylidene-(or
alkenylidene)-pyrrolidines from simple, readily available starting materials (Scheme 25).\(^\text{68}\) This
one-pot process is initiated by a conjugate addition of a propargylamine to a \(\text{gem}\)-diactivated
olefin subsequently followed by a carhopalladation involving an aryl halide (or vinyl triflate).

\[
\text{R}^1 \text{R}^2 \text{YH} + \text{EWG}^2 \text{EWG} \rightarrow \text{R}^1 \text{R}^2 \text{R}^3 \text{X} \rightarrow \text{ Base Pd} \rightarrow \text{R}^1 \text{R}^2 \text{EWG} \text{EWG} \text{EWG}
\]

\(\text{Y} = \text{O},\text{NR} \quad \text{X} = \text{I, Br, OTf}\)

Scheme 25.

Cadierno et al reported an efficient a one-pot multi-component reaction for the preparation of
fully substituted pyrroles, from readily accessible secondary propargylic alcohols, 1,3-dicarbonyl
compounds and primary amines (Scheme 26).\(^\text{69}\) The reaction is catalyzed by the system \([\text{Ru}(\eta^3-2-
\text{C}_5\text{H}_5\text{Me})(\text{CO})]\) \([\text{SbF}_6]/\text{CF}_3\text{CO}_2\text{H}\) (dpf: 1,1'-bis(diphenylphosphanyl)ferrocene). The
reaction involves initial propargylation of the 1,3-dicarbonyl compound promoted by \(\text{CF}_3\text{CO}_2\text{H}\)
and subsequent condensation between the resulting \(\gamma\)-keto alkyne and the primary amine to afford
a propargylated \(\beta\)-enamino ester or ketone, which undergoes a ruthenium- catalyzed 5-exo-dig
annulation to form the final pyrrole.
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

\[
\begin{align*}
\text{HO} & \quad \equiv \quad \text{H} \\
\text{R} & \quad + \quad \text{O} \quad \text{O} \quad \text{R}^1 \quad + \quad \text{R}^2 \quad \text{NH}_2 \quad \text{CF}_3 \text{COOH (50 mol%)} \quad \text{Catalyst (5 mol%)} \quad \text{THF}
\end{align*}
\]

\[
\begin{align*}
\text{Catalyst} & \quad = \quad \text{dppf: 1,1'-bis(diphenylphosphanyl)ferrocene).}
\end{align*}
\]

Scheme 26.
Alizadeh et al have developed an effective route to maleimides, which involves the reaction of an enamine derived from the addition of a secondary amine to a dialkyl acetylenedicarboxylate with an arylsulfonyl isocyanate (Scheme 27). 70

\[
\text{HO} \quad \text{OEt} \quad \text{Reflux}
\]

Scheme 27.
The four-component reaction of ethyl 4-chloroacetoacetate with aromatic aldehydes and ammonium acetate in a 1:2:1 molar ratio provided a simple and rapid access to highly functionalised pyrrolidines, ethyl 1-acetyl-4-hydroxy-5-[hydroxy(aryl)methyl]-2-aryl-2,3-dihydro-1H-pyrrole-3-carboxylates stereoselectively (Scheme 28). 71

\[
\begin{align*}
\text{Cl} & \quad \text{O} \quad \text{OEt} \quad + \quad 2 \quad \text{ArCHO} \quad + \quad \text{NH}_4 \text{OAc} \quad \text{EtOH Reflux}
\end{align*}
\]

Scheme 28.
1.4.1.2. Furan derivatives
1.4.1.2.1. Furan derivatives via isocyanide based MCRs
Reaction of dimethyl acetylenedicarboxylate (DMAD) with isocyanides or with in situ generated carbenes yields a zwitterionic species. The zwitterionic species is highly reactive and is trapped by aldehydes and quinones to yield dihydrofuran derivatives in good yields. 72 The reaction is quite simple. All the three starting materials DMAD, isocyanide and aldehydes or ketone are taken in stoichiometric amounts in dry benzene or toluene and refluxed to get highly functionalized furan derivatives. From the diversity point of view the isocyanide could be aliphatic or aromatic, aldehydes may also be taken aliphatic or aromatic. The reaction is not good.
with simple ketone but gives good yields with activated ketones like isatins,\(^{73}\) 1,2-diketones\(^{74}\) and \(\alpha\)-keto cyanides (Scheme 29).\(^{75}\)

\[
\begin{align*}
\text{COO}_2\text{Me} + \text{RNC} & \rightarrow \text{MeOOC} \equiv \text{C} \equiv \text{COO}_2\text{Me} \\
\text{COO}_2\text{Me} + \left[ \text{MeOOC} \equiv \text{C} \equiv \text{COO}_2\text{Me} \right] & \rightarrow \text{RCHO} \\
\text{COO}_2\text{Me} + \left[ \text{MeOOC} \equiv \text{C} \equiv \text{COO}_2\text{Me} \right] & \rightarrow \text{RCHO}
\end{align*}
\]

Scheme 29.

The reaction of isocyanides, aldehydes and enols (1,3-dicarbonyls) is also a very popular method for the synthesis of furan derivatives. The reaction probably proceeds with initial formation of an intermediate by the reaction of aldehydes and isocyanides which is then attacked by enols to yield the furan derivatives. Teimouria et al reported a regioselective three-component condensation reaction of 2-hydroxy-1,4-naphthoquinone, isocyanides and a variety of aldehydes yielding to linear naphtho[2,3-b]-furan-4,9-dione derivatives (Scheme 30).\(^ {76}\)

\[
\begin{align*}
\text{RNC} + \text{R}^1\text{CHO} + \text{OH} & \rightarrow \text{Toluene, reflux} \\
\text{RNC} + \text{R}^1\text{CHO} + \text{OH} & \rightarrow \text{H}_2\text{O, 75 °C}
\end{align*}
\]

Scheme 30.

Shabani et al reported an environment-friendly three component condensation reactions of \(N,N\)-dimethylbarbituric acid, 4-nitrobenzaldehyde and alkyl or aryl isocyanides to afford the corresponding furo[2,3-\(d\)]pyrimidine-2,4(1\(H\),3\(H\))-diones, in water, in high yields (Scheme 31).\(^ {77}\)

\[
\begin{align*}
\text{RNC} + \text{R}^1\text{CHO} + \text{H}_2\text{O} & \rightarrow \text{H}_2\text{O, 75 °C} \\
\text{RNC} + \text{R}^1\text{CHO} + \text{H}_2\text{O} & \rightarrow \text{H}_2\text{O, 75 °C}
\end{align*}
\]

Scheme 31.
Fan et al reported a piperidine catalyzed reaction of cyclohexyl isocyanide with various aldehydes and 1,3-dicarbonyl compounds. The protocol offers facile and efficient synthesis of 5-hydroxy-2H-pyrrol-2-one derivatives from readily available starting materials in high yields (Scheme 32).

\[
\text{CyNC} + R^1\text{CHO} + \text{R}^2\text{COOR}^3 \xrightarrow{\text{Toluene, Piperidine, 100 °C}} \text{Scheme 32.}
\]

5-Acylamino butenolides were assembled by a multi-component reaction (MCR) of isocyanides, glyoxals, and acetophosphonic acid diethyl esters, followed by an intramolecular Wittig-type reaction. The reaction can be performed either in one pot or with the isolation of the intermediate Passerini product. This versatile reaction offers three independent inputs displayed in the final product (Scheme 33).

\[
\text{Scheme 33.}
\]

1.4.1.2.2. Furan derivatives via transition metal mediated MCRs

Many transition metals mediated MCRs are now available for the synthesis of furan derivatives. The one-pot assembly of 4-alkoxy-3-iodo-2-pyridones, terminal alkynes, and organic halides has been achieved by integration of two sequential palladium-mediated cross-coupling reactions-Sonogashira and Wacker-type heteroannulation processes-and subsequent deprotection of the alkoxy group to afford furo[2,3-b]pyridones (Scheme 34).

\[
\text{Scheme 34.}
\]

A one-pot reaction between equimolecular amounts of various propargyl alcohols, Michael acceptors and unsaturated halides (or triflates) in the presence of a palladium (0) catalyst provides a simple and flexible entry into highly substituted 3-arylidene-(or 3-alkenylidene-) tetrahydrofurans (Scheme 35). The efficiency of this palladium-mediated three-component reaction has been shown to be strongly influenced by the nature of the catalyst system, and in this...
regard, a palladium(0) catalyst generated in situ by reduction of PdCl(PPh$_3$)$_2$ with n-butyllithium has been found particularly effective.$^{81}$

Scheme 35.

A three-component cyclization-coupling reaction catalyzed by palladium has been developed, producing poly substituted furans in good yields from readily available substrates (Scheme 36).$^{82}$

Scheme 36.

Reaction of zirconacyclopentenes with 2 equiv. of the same aldehydes in the presence of 1 equiv. of CuCl affords tetrahydrofuran derivatives in good isolated yields upon hydrolysis with aqueous 3 N HCl (Scheme 37). Oxazirconacycloheptenes, generated in situ from zirconacyclopentenes with one aldehyde was found to be the reactive intermediate. When treated with a second aldehyde and CuCl, an oxazirconacycloheptene gave a tetrahydrofuran derivative comprised of four different components involving an alkyne, an ethylene and two different aldehydes, thus providing the first one-pot synthesis of important tetrahydrofuran derivatives from four-components.$^{83}$

Scheme 37.

Duan et al reported a three-component cyclization-coupling reaction of propargyl carbonate, ψ-keto esters, and aryl iodide catalyzed by palladium, producing poly substituted furans in good yields (Scheme 38).$^{84}$ This three-component cyclization-coupling protocol provides an efficient access to a variety of polysubstituted furans and shows some advantages in terms of its simple operation, easily availability, and diversity of the starting material.
Satoh et al. synthesized naphthofuran-2(3H)-one analogues by three-component tandem reaction using 1- or 2-naphthols, aldehydes, and carbon monoxide in the presence of a palladium catalyst (Scheme 39).

The reaction of N-alkyl-3-oxobutanamides, derived from the addition of amines to the diketene, and dibenzoylacetylene in the presence of triphenylphosphine results the synthesis of highly functionalized furans (Scheme 40).

Thiophene derivatives are synthesized by Gewald Reaction. It is a multi-component condensation between sulfur, an α-methylene carbonyl compound and an α-cyanoester resulting to the formation of 2-aminothiophenes (Scheme 41).
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

Scheme 42.
Recently a microwave-promoted synthesis of 2-aminothiophenes by multi-component reactions of a ketone with an active nitrile and elemental sulfur under KF-alumina catalysis was described (Scheme 43). 87

Scheme 43.

1.4.2. Five membered heterocycles containing two heteroatoms

1.4.2.1. Pyrazolidines

Protonation of the highly reactive 1:1 intermediate produced in the reaction between alkyl isocyanides and electron-deficient acetylenic esters with phthalhydrazide, leads to a imylisonitrilium cation, which undergoes an addition reaction with the conjugate base of the phthalhydrazide to produce dialkyl 3-(alkyl amino)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-1,2-dicarboxylates in fairly good yields at room temperature (Scheme 44). 88

Scheme 44.

Xie et al have synthesized pyrazoles via a sequential one-pot, three-component reaction of iodochromone, arylboronic acid, and hydrazine by Suzuki coupling and condensation (Scheme
This method provides facile construction of these heterocycle libraries that are applicable for biological screening.

Scheme 45.

Mori et al. reported a four component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide, and an aryl iodide to furnish pyrazole or isoxazole derivatives in the presence of a palladium catalyst (Scheme 46). The reaction proceeds at room temperature and an ambient pressure of carbon monoxide in an aqueous solvent system. Hydrazine and hydroxylamine play dual roles as a component of ring formation and an activating agent for the carbonylative coupling reaction.

Scheme 46.

1.4.2.2. Imidazolidines

Due to their diverse range of biological activities, imidazo-heterocycles are recognized as privileged structures making these structural motifs attractive targets for library preparation. Rousseau et al. reported a zinc chloride catalyzed the one-pot, three component synthesis of imidazo [1,2-a] pyridines from a range of substrates using either conventional heating or microwave irradiation (Scheme 47). This methodology affords a number of imidazo [1,2-a] pyridines in reasonable yields and short reaction times without any significant optimization of the reaction conditions.

Scheme 47.
Bencsik et al synthesized a large collection of highly pure imidazo[1,2-α]heterocycles by expanding three component coupling of aldehydes, 2-amino heterocycles, and isonitriles (Scheme 48). Global diversity around these heterocycles was further enhanced in two ways: first through regioselective partial reduction of imidazo[1,2-α]pyrazines to afford the tetrahydro variants and second through development of novel and extremely mild conditions for Mannich bond formation at the C-3 position of imidazo[1,2-α]pyridines. Through in silico evaluation of the drug-like properties of the final library, they achieved a high value screening library of approximately 7500 compounds with a 92% rule-of-five compliance.

Scheme 48.

Alizadeh et al described an effective route to functionalized hydantoin derivatives involving the reaction of a urea derivative resulting from the addition of a primary amine to an arylsulfonyl isocyanate, and an alkyl propiolate or dialkyl acetylenedicarboxylate in the presence of triphenylphosphine (Scheme 49). The reactive 1:1 intermediate obtained from the addition of triphenylphosphine to the alkyl propiolate or dialkyl acetylenedicarboxylate was trapped by NH-acids such as the urea derivative to produce functionalized hydantoin derivatives.

Scheme 49.

Illgen et al described a three-component, one-pot condensation yielding 1H-imidazol-4-yl-pyridines from aldehydes, o-picolylamines, and isocyanides. They have investigated the scope and limitations of the reaction (Scheme 50).
Porwal et al described a multi-component reaction that converts aryl/heteroaryl aldehydes efficiently into arylmethylene 2-thiohydantoins (Scheme 51).\(^\text{95}\)

\[
\text{RCHO} + \text{H}_2\text{NCH}_2\text{COOH} + \text{KSCN} \xrightarrow{\text{Ac}_2\text{O}} \text{R} = \text{N} = \text{S}
\]

**Scheme 51.**

Matsuoka et al have synthesized enantiopure 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles by using the multi-component condensation of a 1,2-dicarbonyl compound, an aldehyde, a 1,2-amino alcohol, and ammonium acetate (Scheme 52).\(^\text{96}\)

\[
\text{R}_1\text{R}_2\text{N} = \text{H}_2\text{N}_\text{OH} \xrightarrow{\text{NH}_4\text{OAc}, \text{MeOH, 80°C}} 5\text{h} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{N} = \text{O}
\]

**Scheme 52.**

### 1.4.2.3. Isoxazoles and Oxazoles

Isoxazolidines are synthesized by 1,3-dipolar cycloaddition of nitrones derived in situ from aldehydes and aryl hydroxylamine, with electron deficient olefins (Scheme 53). The reaction is accelerated by 1-butyl-3-methylimidazolium based ionic liquids and improved yields of isoxazolidines are obtained with high regio- and diastereoselectivity.\(^\text{97}\)

\[
\text{R} = \text{CHO} + \text{PhNHOH} \rightarrow \left[ \text{R} = \text{N} = \text{O} \right] \xrightarrow{\text{EWG} = \text{CN, COO}\text{Me, COMe}} \text{R}^1\text{E}\text{W}\text{G}
\]

**Scheme 53.**

Lijun et al reported an efficient and general one-pot, four-component condensation resulting to the formation of substituted 2-oxazolines, which are found in several families of bioactive natural products (Scheme 54).\(^\text{98}\) In this reaction the Passerini product is also obtained as side product but increasing the quantities of ammonia and benzoic acid and by replacing methanol as solvent with 2,2,2-trifluoroethanol, the yield of Ugi product could be enhanced. This multi-component synthesis reported here rapidly assembles promising lead compounds containing this heterocyclic system for use in drug discovery endeavors.
Maghsoudlou et al reported a three component reaction of 2-fluorobenzaldehyde, phenanthroline and cyclohexyl or 2,6-dimethylphenyl isocyanide resulting to the formation of N-cyclohexyl-10-(2-fluorophenyl)-8aH-oxazolo[3,2-a][1,10]phenanthroline and N-(2,6-dimethylphenyl)-10-(2-fluorophenyl)-8aH-oxazolo[3,2-a][1,10]phenanthroline (Scheme 55).99

Wang reported a one-pot, isocyanide based MCR leading to the synthesis of oxazole derivatives (Scheme 56).100

Black et al reported a copper(I) and zinc(II) catalyzed routes to construct secondary propargylamides in one-pot procedures from aldehydes, LiN(TMS)$_2$, acid chlorides, and alkynes. This reaction has been subsequently used to provide a one-pot synthesis of oxazoles from four simple building blocks (Scheme 57).101
1.4.2.4. Thiazoles

Substituted 2-acyloxyethyl thiazoles have been assembled by a multi-component reaction of methyl 3-(N,N-dimethylamino)-2-isocyanoacrylate, aldehydes and thiocarboxylic acid under Lewis acid catalysis (Scheme 58). 102

\[
\text{Scheme 58.}
\]

Reaction of a cyclic amino acid with acetylene dicarboxylic acid esters and acetic anhydride above 100 °C yields a 1,3-dihydropyrrolo[1,2-c]thiazole derivative which has been used in the synthesis of substituted pyrroles (Scheme 59). 103

\[
\text{Scheme 59.}
\]

Srivastava et al synthesized 4-thiazolidinones by DCC mediated three-component reaction of amine, aldehyde and mercaptoacetic acid (Scheme 60). 104 The products were obtained in quantitative yields and amenable to scale-up operations. The yields of the thiazolidinones were independent of the nature of the reactants.

\[
\text{Scheme 60.}
\]

Dubreuil et al prepared a small library of 4-thiazolidinones by a one-pot three-component condensation under microwave dielectric heating (Scheme 61). 105

\[
\text{Scheme 61.}
\]
1.4.2.5. Oxaphospholes

Esmaeili et al.\textsuperscript{106} and Yavari et al.\textsuperscript{107} simultaneously reported a three component reaction of N-alkyl isatin, acetelene dicarboxylic acid ester and \((\text{PPh}_3)_3\) resulting to the formation of spiro-2,5-dihydro-1,2-\(\lambda^5\)-oxaphospholes (Scheme 62). The procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme62.png}};
\end{tikzpicture}
\end{center}

\textit{Scheme 62.}

1.4.2.6. Dioxolanes

Nair reported a three-component reaction of acyclic carbonyl ylides generated from dicarbomethoxycarbene and aldehydes with 1,2- and 1,4-diones is described. The reaction afforded the corresponding spiro-dioxolanes in good yields (Scheme 63).\textsuperscript{108}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme63.png}};
\end{tikzpicture}
\end{center}

\textit{Scheme 63.}

1.4.3. Five membered heterocycles containing three heteroatoms

1.4.3.1. Triazoles

1,2,3-Triazoles are generally synthesized by transition metal catalyzed 1,3-dipolar cycloaddition reaction of terminal alkynes with in situ generated alkyl azides. Alkyl azides are generated by the reaction of trimethylsilyl azide with secondary alcohols\textsuperscript{109} allyl carbonates\textsuperscript{110} and sodium azide with alkyl bromide (Scheme 64).\textsuperscript{111}
1,2,4-triazolidines are synthesized by a ruthenium porphyrin catalyzed three-component coupling reaction of α-diazo esters, imines and dialkyl azodicarboxylates (Scheme 65). The reaction proceeds with in situ generation of azomethine ylides from adiazo esters and imines. Stereoselective 1,3-dipolar cycloaddition reactions of the azomethine ylides with dialkyl azodicarboxylates gives the corresponding 1,2,4-triazolidines in good yields. Using chiral 8-phenylmenthanol α-diazo ester as the carbenoid source, chiral 1,2,4-triazolidines have been obtained in good diastereoselectivity.

Scheme 65.

1.4.3.2. Oxadiazoles

Adib et al synthesized 1,2,4-oxadiazoles from a one-pot, three-component reaction between nitriles, hydroxylamine, and aldehydes under microwave irradiation and solvent-free conditions in excellent yields (Scheme 66).
1.5. Six membered heterocycles

1.5.1. Six membered heterocycles having one heteroatom

1.5.1.1. Pyridine derivatives

Six membered heterocycles containing single nitrogen are pyridine derivatives. Biologically the most important simple single nitrogen containing heterocycle is 1,4-dihydropyridine. 1,4-Dihydropyridines (1,4-DHPs) are a class of model compounds of NADH coenzyme which mediates hydrogen transfer reactions in biological systems. 1,4-DHPs have been established as one of the first line drugs for treatment of hypertension because of their promising depressor effect and relatively good tolerability. Felodipine, amlodipine, nifedipine and nicardipine (Fig. 8) are among the best selling drugs in the pharmaceutical industry. 1,4-DHPs have been extensively studied because of the biological significance of these compounds to the NADH redox process as well as their therapeutic functions for treatment of a variety of diseases, such as cardiovascular disorders, cancer and AIDS.

\[ RCHO + 2 \text{R}^1\text{R}^2\text{COOCR}^2 + \text{NH}_3 \rightarrow \text{R}^2\text{OOCR}^2 \]

Scheme 67.

Figure 8.
The Hantzsch pyridine synthesis or Hantzsch dihydropyridine synthesis is a multi-component organic reaction between an aldehyde such as formaldehyde, 2 equivalents of a α-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia (Scheme 67).
The initial reaction product is a dihydropyridine which can be oxidized in a subsequent step to a pyridine. The driving force for this second reaction step is aromatization (Scheme 68).

\[
\text{R}^2\text{OOC} - \text{C} - \text{COOR}^2 \xrightarrow{\text{HNO}_3} \text{R}^2\text{OOC} - \text{C} - \text{COOR}^2 \xrightarrow{1) \text{KOH}} \text{R}^1\text{N} - \text{R}^1 \xrightarrow{2) \text{CaO, heat}} \text{R}^1\text{N} - \text{R}^1
\]

**Scheme 68.**

We have demonstrated the effect of ultrasonic irradiation over Hantzsch dihydropyridine synthesis in aqueous micelles (Scheme 69).\(^{114}\)

\[
\text{R}^1\text{CHO} + 2\text{CO}_2\text{O} + \text{NH}_4\text{OAc} \xrightarrow{\text{p-TsOH, Aq. Micelles}} \text{R}^1\text{OOC} - \text{C} - \text{COOR}^1
\]

**Scheme 69.**

Direct aromatization of 1,4-dihydropyridines has been reported using ferric chloride\(^{115}\) or aluminium chloride and subsequent oxidation with H\(_2\)O\(_2\) under microwave irradiation\(^{116}\) in a one-pot synthesis in water. The four component Hantzsch reaction has been modified to a three component reaction by taking amino crotonate in the place of ammonia and acetoacetate ester (Scheme 70).\(^{117}\)

\[
\text{NHBOc} + \text{CHO} + \text{COOBOc} + \text{ROOC} - \text{C} - \text{COOR} \xrightarrow{\text{H}_2\text{N}} \text{NHBOc} + \text{ROOC} - \text{C} - \text{COOBn}
\]

**Scheme 70.**

In Hantzsch reaction two molecules of acetoacetate ester are used resulting in the formation of symmetrical compound. We replaced the second molecule of acetoacetate ester by cyclic 1,3-diketones, thus, unsymmetrical product (polyhydroquinoline derivative) was formed. The reaction was catalyzed by organocatalyst like proline and cinchona alkaloids. The catalytic efficiency of various small organocatalysts such as L-proline, trans-4-hydroxy-L-proline, L-thiaproline, DL-phenylglycine, and cinchonidine was studied under aqueous, organic, and solvent-free conditions (Scheme 71).\(^{118}\) We have also carried out the enzymatic variant of this reaction. Bakers' yeast was found to catalyze the four component reaction of aldehyde, dimedone, acetoacetate ester and ammonium acetate to form the polyhydroquinoline derivatives.\(^{119}\)
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

We have successfully carried out an organocatalyzed three-component reaction of cinnamaldehydes, acetoacetate esters and anilines resulting to the formation of 1,4-dihydropyridines under solvent free conditions (Scheme 72).

Scheme 72.

Quinoline derivatives are synthesized by a well known Povarov reaction, a chemical reaction described as a formal cycloaddition between an aromatic imine and an alkene. The imine in this organic reaction is a condensation reaction product from an aniline type compound and a benzaldehyde type compound. The alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons. Such alkenes are enol ethers and enamines. The reaction mechanism for the Povarov reaction to the quinoline is outlined in scheme 73. In step one aniline and benzaldehyde react to the Schiff base in a condensation reaction. The Povarov reaction requires a lewis acid such as boron trifluoride to activate the imine for an electrophilic addition of the activated alkene. This reaction step forms an oxonium ion which then reacts with the aromatic ring in a classical electrophilic aromatic substitution. Two additional elimination reactions create the quinoline ring structure.

Scheme 73.

5-Methoxy substituted quinolines are a common structural feature in a number of biologically active quinoline alkaloids, for example 9-methoxycamptothecin, 9-methoxymappicine ketone and S-9-methoxymappicine. This latter alkaloid is also known as nothapodytine A (Figure 9).
Figure 9. Luotonin A precursor and a range of bioactive quinoline alkaloids isolated from nothapodytes foetida with and without substituent at C9.

The reaction depicted in scheme 74 illustrates the Povarov reaction with an imine and an enamine in the presence of yttrium triflate as the lewis acid. This reaction is regioselective because the iminium ion preverentially attacks the nitro ortho position and not the para position. The nitro group is a meta directing substituent but since this position is blocked, the most electron rich ring position is now ortho and not para. The reaction is also diastereoselective because the enamine addition occurs with a preference for trans addition without formation of the cis isomer.

**Scheme 74. regio- and diastereoselective Povarov reaction**

An efficient liquid-phase synthesis technique for the construction of 2,3-dihydro-4-pyridones on soluble polymer support has been developed, which utilized one-pot reaction of Danishefsky’s diene with aldehydes and polymer-supported amine (Scheme 75).

**Scheme 75.**

Shindoh et al reported a Tf₂NH catalyzed multi-component Povarov reaction aniline, aldehyde, and allylsilane, to provide substituted quinolines (Scheme 76).
Scheme 76.

Pyrindines and quinolines were synthesized in good yields in a one-pot three-step four-component process by a coupling-isomerization-Stork-enamine alkylation-cyclocondensation sequence of an electron poor (hetero)aryl halide, a terminal propargyl alcohol, a cyclic N-morpholino alkene and ammonium chloride (Scheme 77). 125

\[
\text{Ar}^1 - \text{Hal} + \text{CHO} + \text{TIPS} \xrightarrow{\text{Ti}_2\text{NH (10 mol\%)} \text{ Toluene, 60}\,^{\circ}\text{C}} \text{Ar}^1\text{NH} + \text{TiPS}
\]

\[
\text{Ar}^1 = \text{EWG(het)aryl} \quad \text{Ar}^2 = \text{(het)aryl}
\]

Scheme 77.

Microwave-assisted three-component cyclocondensation of barbituric acids, benzaldehyde and alkyl nitriles proceeds in the absence or presence of triethylamine to afford pyrano[2,3-d]pyrimidines. Similarly aminouracils or 6-hydroxyaminouracils were synthesized under identical conditions to yield pyrido[2,3-d]pyrimidines, all in high yields (Scheme 78). 126

\[
\text{PhCHO} + \text{X} = \text{NH}_2, \text{NHOH} \xrightarrow{\text{MW}} \text{PhN} + \text{R}^2\text{CH}_2\text{CN}
\]

Scheme 78.

Polysubstituted pyridines are prepared in good yield and with total regio-control by the one-pot reaction of an alkynone, 1,3-dicarbonyl compound and ammonium acetate in alcoholic solvents (Scheme 79). This three-component heteroannulation reaction proceeds under mild conditions in the absence of any additional acid catalyst and has been used in the synthesis of dimethyl
sulfomycinamate, the acidic methanolation degradation product of the sulfomycin family of thiopeptide antibiotics.\textsuperscript{127}

\[
\text{R}^1\text{OC} \quad \text{COR}^3 + \quad \text{NH}_2\text{OAc} \quad \xrightarrow{\text{Ethanol, reflux} \ \ 24\text{h}} \quad \text{R}^1\text{OC} \quad \text{COR}^3
\]

\textbf{Scheme 79.}

A three-component reaction involving isoquinoline, dimethyl butynedioate and electrophilic styrenes has been developed (Scheme 80). The reaction proceeds through a Huisgen 1,4-dipolar cycloaddition pathway.\textsuperscript{128}

\[
\begin{array}{c}
\text{THF, rt} \quad 23\text{h} \quad 2:1 \\
\end{array}
\]

\textbf{Scheme 80.}

Evdokimov et al have developed a three-component reaction of salicylaldehydes, thiols and 2 equiv of malononitrile that leading to the formation of a series of compounds incorporating 2,4-diamino-3-cyano-5-sulfanylbenzopyran[2,3-b]pyridine framework (Scheme 81).\textsuperscript{129} Benzopyran[2,3-b]pyridine is an important privileged medicinal scaffold.

\[
\begin{array}{c}
\text{R}^1\text{VCHO} \quad \text{I.b} + \quad \text{R}^1\text{OH} \quad \text{RSH} \\
\end{array}
\]

\textbf{Scheme 81.}

A one-pot, four-component reaction of 1-(phenylsulfinyl)- or 1-(4-chlorophenylsulfmyl)propan-2-one, aromatic aldehydes and ammonium acetate in a 1:2:1 molar ratio affords a series of 2,6-diaryl-2,3-dihydro-1H-pyrind-4-ones (Scheme 82). This reaction proceeds presumably via a double Mannich reaction–elimination tandem sequence.\textsuperscript{130}

\[
\begin{array}{c}
\xrightarrow{\text{Et}_3\text{N} \quad \text{EtOH, reflux}} \\
\end{array}
\]

\textbf{Scheme 82.}
Trimethylchlorosilane (TMSCI) promoted multi-component reaction (MCR) of ethylenediamine(s), diverse carbonyl compounds, and isocyanides has been developed for the synthesis of a variety of highly substituted 3,4,5,6-tetrahydropyrazin-2-amines including corresponding spirocyclic compounds (Scheme 83).

\[
\text{TMSCI} \quad (\pm) \quad \text{mediated by trifluoromethanesulfonic acid, ethynyl ketene-S,S-acetals was reacted in a one-pot procedure with various arylamines and aldehydes under mild conditions to give the corresponding quinoline derivatives in good to high yields via a consecutive arylimine formation, regiospecific aza-Diels-Alder (Povarov) reaction, and reductive amination (Scheme 84).}
\]

Privileged medicinal scaffolds based on the structures of 2-amino-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydropyridines have been prepared via a single-step, three-component reaction of aldehydes with various thiols and malononitrile (Scheme 85). Mechanistic studies revealed that 1,4-dihydropyridines undergo oxidation by the intermediate Knoevenagel adducts rather than by air oxygen. Although the latter process undermines the yields of pyridines, it results in the formation of substituted enaminonitriles, promising anti-inflammatory agents.
Chapter 1  
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds  
2009

Three-component reactions with ortho-alkynylbenzaldehydes, primary amines, and pronucleophiles (Nu-H), such as CHCl₃, proceeded to give 1,2-dihydroisoquinoline derivatives in good to high yields in the absence of any catalysts under mild reaction conditions (Scheme 86). 134

\[
\text{CHO} + R'NH_2 + \text{NuH} \rightarrow \text{Nu-R'} 
\]

Scheme 86.

1.5.1.2. Pyran derivatives

Jia et al have described a simple one-pot three-component reaction involving isatin, activated methylene reagent, and 1,3-dicarbonyl compounds for the synthesis of a series of spirooxindoles derivatives in water (Scheme 87). 135

\[
\begin{align*}
\text{R}^2 & \text{R}^3 \quad \text{X} \quad \text{OH} \\
\text{I} + \text{R}^4 & \text{R}^5 \\
\text{H}_2\text{O, TEBA} & 60^\circ\text{C} \\
\text{R}^2 & \text{R}^3 \quad \text{X} = \text{CN}, \text{COOCH}_3 \\
\end{align*}
\]

Scheme 87.

The reaction of an aldehyde, malononitrile and a phenol in water at reflux in the presence of cetyltrimethylammonium chloride (CTACl) as catalyst affords a one-pot synthesis of 2-amino-2-chromenes (Scheme 88). 136

\[
\begin{align*}
\text{R}^3 & \text{R}^2 \quad \text{OH} \\
\text{R}^4 & \text{R}^5 \\
\text{R}'\text{CHO} + \text{CH}_2(\text{CN})_2 & \xrightarrow{\text{CTACl, H}_2\text{O}} 110^\circ\text{C, 6h} \\
\text{R}^3 & \text{R}^2 \quad \text{NH}_2 \\
\end{align*}
\]

Scheme 88.

Several bis-pyran-1,4-benzoquinones have been synthesized by a double domino Knoevenagel hetero Diels–Alder reaction (Scheme 89). 137 The synthetic approach is highly efficient allowing the construction of complex polycyclic scaffolds with six new σ-bonds. These reactions performed more efficiently and more rapidly using microwave irradiation.
Sodium bromide catalysed three-component cyclocondensation of aryl aldehydes, alkyl nitriles and dimedone proceeds under microwave irradiation in solvent free conditions to give highly functionalised tetrahydrobenzo[b]pyrans in excellent yields (Scheme 90).\(^\text{138}\)

\[
\text{RCHO} + \text{R'}\text{CH}_2\text{CN} + \text{O} \quad \xrightarrow{\text{MW}} \quad \text{NaBr} \quad \xrightarrow{\text{O}} \quad \text{R} \quad \text{R'} \quad \text{NH}_2
\]

\(R' = \text{CN, CONH}_2, \text{COOEt}\)

**Scheme 90.**

A new type of multi-component reaction is described in which five organic molecules form a cyclohexane ring. Aryl aldehydes, malononitrile and acetone in the presence of a catalytic amount of sodium acetate are stereoselectively cyclized into cis-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles in 30–60% yields (Scheme 91).\(^\text{139}\)

**Scheme 91.**

Concise synthesis of defucogilvocarcin M was achieved via the [2 + 2 + 2] approach to \(\alpha\)-phenylnaphthalene structure (Scheme 92).\(^\text{140}\)
Isocyanides, dimethyl acetylenedicarboxylate, and cyclobutene-1,2-diones react in one-pot to afford novel spirocyclic compounds with double insertion of the isocyanide (Scheme 93).  

![Scheme 93.](image)

**1.5.2. Six membered heterocycles having two heteroatoms**

**1.5.2.1. Pyrimidine derivatives**

The most studied MCR derived six membered heterocycles containing two nitrogens are 3,4-dihydropyrimidinone derivatives which are also known as Biginelli compounds. The compounds exhibit a broad range of biological activities like calcium channel modulator, α-1a antagonist, antihypertensive, antiviral and anticancer (Figure 10). Thus a plethora of methods have been developed for the synthesis of Biginelli compounds.

![Figure 10. Biologically active 3,4-dihydropyrimidinone(thione)](image)

We have synthesized 3,4-dihydropyrimidinones via a TiCl₄-MgCl₂ catalyzed three component condensation of aldehyde, 2-keto ester and urea/thiourea (Scheme 94). We have also developed the enzymatic variant of the reaction.

![Scheme 94.](image)

Chen et al have successfully synthesized asymmetric 3,4-dihydropyrimidinones using chiral binaphthyl phosphate as catalyst. Wang et al reported an iron (III) catalyzed the three-
component Biginelli-like cyclocondensation reaction to afford the corresponding 5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones in high yields (Scheme 95). Ferric chloride catalyzed Biginelli-like reactions of urea, aldehydes and ketones furnished diaryl-3,4-dihydropyrimidin-2-(1H)-ones.\footnote{145}

![Scheme 95.](image)

4,6-Diaryl-3,4-dihydropyrimidine-2(1H)-thione were synthesized in a sequential one-pot three component reaction of aldehydes, acetophenones and thiourea in alkaline ethanol (Scheme 96).\footnote{146} These compounds exhibited in vitro antitumour activity with moderate to excellent growth inhibition against a panel of 60 cell lines of leukemia, non-small cell lung cancer melanoma, ovarian cancer, prostate cancer and breast cancer.

![Scheme 96.](image)

Dandia et al have developed a one-pot solvent-free procedure for the synthesis of fluorinated 2,3-disubstituted quinazolin-4(3H)-ones by three-component cyclocondensation of anthranilic acid, phenyl acetyl chloride and substituted anilines under microwave irradiation (Scheme 97). The reaction is generalized for o-, m- and p-substituted anilines with electron-donating and -withdrawing groups to give quinazolin-4(3H)-ones. Synthesized compounds have been screened for their anti-fungal activity.\footnote{147}

![Scheme 97.](image)

Spiro-fused heterocycles were synthesized in good to high yields by a pseudo four-component reaction of an aldehyde, urea and a cyclic β-diester or a β-diamide such as Meldrum’s acid or...
barbituric acid derivatives using microwave irradiation under solvent-free conditions (Scheme 98).\textsuperscript{148}

![Scheme 98.](image)

An acid catalyzed three component reaction of 2-oxosuccinic acid, urea and aldehyde has been developed and exploited to expeditiously synthesize a diverse set of 5-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones in high yield (Scheme 99). Electron-rich as well as electron-deficient aldehydes proved to be excellent substrates for the cyclo-condensation. Pyrimidones were prepared using standard cyclization conditions and more effectively synthesized using a unique set of conditions (i.e., TFA in refluxing dichloroethane). The carboxylic acid appendage on C(6) offers functionality capable of a wide variety of transformations.\textsuperscript{149}

![Scheme 99.](image)

Shabani et al have developed a multi-component synthesis of highly substituted 1, 6-dihydropyrazine-2,3-dicarbonitrile derivatives starting from simple and readily available inputs. Simply stirring an ethanol solution of 2,3-diaminomaleonitrile, a ketone, and an isocyanide in the presence of a catalytic amount of p-toluenesulfonic acid provides highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in good to excellent yields at ambient temperature (Scheme 100).\textsuperscript{150}

![Scheme 100.](image)

The 1,4-dipole derived from isoquinoline and DMAD has been shown to react readily with N-tosylimines resulting in the diastereoselective synthesis of 2H-pyrimido [2,1-a] isoquinoline derivatives (Scheme 101).\textsuperscript{151}
Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds
2009

Scheme 101.
2,4,6-Tri(hetero)aryl-substituted pyrimidines has been synthesized in a three-component one-pot process based upon a coupling- isomerization sequence of an electron-poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with amidinium salts (Scheme 102).

Scheme 102.
TMS-ynones are versatile synthetic equivalents of α-keto aldehydes and can be readily synthesized in an atom-economical fashion by coupling (het) aryl chlorides and (TMS)-acetylene with only one equivalent of triethylamine under Sonogashira conditions. This mild ynone synthesis is a suitable entry to 2,4-disubstituted pyrimidines in the sense of a one-pot three-component reaction, i.e., a coupling-addition- cyclocondensation sequence (Scheme 103).

Scheme 103.
A diastereoselective three-component reactions of 3,4-dihydro-(2H)-pyran with urea/thiourea-aldehyde mixtures leading to hexahydro-4-phenyl-1H-pyran[2,3-d]pyrimidin-2(8aH)-ones or hexahydro-4-phenyl-1H-pyran[2,3-d]pyrimidine-2(8aH)-thiones were developed by Zhu et al (Scheme 104). The authors have proposed that reaction proceed via intermediacy of N-acyliminium ions which undergo a hetero [4 + 2] cycloaddition with alkenes.

Scheme 104.
1.5.2.2. Oxazine derivatives

The reaction between alkyl or aryl isocyanides and dialkyl acetylene dicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2H-imidazol-2-one provides a simple one-pot entry into the synthesis of polyfunctional imidazo[2,1-b][1,3]oxazine derivatives of potential synthetic and pharmaceutical interest (Scheme 1.05).155

\[
\text{Scheme 1.05.}
\]

A new one-pot procedure for the efficient synthesis of novel 3-substituted morpholin-2-one-5-carboxamide derivatives using commercially available glycolaldehyde dimer as a bifunctional component with various α-amino acids and isocyanides by the Ugi five-center three-component reaction (U-5C-3CR) has been developed (Scheme 1.06).156

\[
\text{Scheme 1.06.}
\]

The reaction of nitrones, formed in situ by reaction of hydroxylamines with aldehydes, with 1,1-cyclopropanediesters results in the formation of tetrahydro-1,2-oxazines via a homo 3 + 2 dipolar cycloaddition (Scheme 1.07). This three-component coupling allows for the formation of a diverse array of cycloadducts with excellent diastereoselectivity (>95%) and yields (66-96%). The procedure has been used in the two-step preparation of congeners of the FR900482 skeleton.157

\[
\text{Scheme 1.07.}
\]

1.5.2.3. Thiazines

MCRs have been successfully applied for the construction of six membered heterocycles containing one nitrogen and one sulphur heteroatom in the ring. The Ugi four-component condensation between 5-oxo-3-thiacarboxylic acids, benzylamines and cyclohexyl isocyanide in methanol gave 5-oxothiomorpholine-3-carboxamides in high yields (Scheme 1.08).158
A three-component reaction of pyridine, thiophthalimide and acyl chloride yielding a tricyclic 1,2-dihydropyridines in good regio- and stereoselectively has been reported. The authors have proposed a mesomeric betaine as a key intermediate for [4+2]-cycloaddition reaction with thiocarbonyl compounds (Scheme 109).

The one-pot, three-component condensation of alkynes, urea or thiourea, and aldehydes results to the formation of 2-amino-4 H-1,3-oxazines or 2-amino-4 H-1,3-thiazines (Scheme 110).

The one-pot, four-component reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)-sulfonyl]acetate, an aromatic aldehyde and pyrrolidine provides a rapid and facile access to new ethyl 3-aryloyl-1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-c][1,4]thiazine-1-carboxylates/diethyl 1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-c][1,4]thiazine-1,3-dicarboxylates (Scheme 111).
1.6. Seven membered and higher heterocycles

One-pot MCRs have been successfully applied in the synthesis of seven membered heterocycles.

1.6.1. Benzodiazepine derivatives

A three-component reaction of aromatic aldehydes, ethylenediamine, and \( \beta \)-keto esters was originally developed by Fujioka et al (Scheme 112).\(^{162} \) The reaction was carried out in dichloroethane using \( p \)-toluene sulphonic acid as catalyst. In this reaction, \( \beta \)-keto esters react at the \( \gamma \)-position which is generally unreactive to produce the seven-membered ring compounds. Products have secondary amines and \( \beta \)-enamino esters, which serve in further fictionalizations to produce molecular diversity.

\[
\text{ArCHO} + \text{NH}_2\text{NH}_2 + \text{\( \beta \)}\text{-keto ester} \rightarrow \text{benzodiazepine derivative}
\]

Scheme 112.

The scope of the reaction was further expanded by taking o-phenylenediamine in the place of ethylenediamine thus leading to formation of 1,5-benzodiazepine derivatives (Scheme 113).\(^{163} \)

\[
\text{Ar}_{\text{NH}_2} + \text{\( \beta \)}\text{-keto ester} + \text{ArCHO} \rightarrow \text{1,5-benzodiazepine}
\]

Scheme 113.

The reaction was further simplified by Jean et al. They carried out the one-pot stereoselective reaction under solvent- and catalyst-free conditions in high yields. This green and experimentally simple sequence results in a high increase in molecular complexity and diversity. Moreover, water is the only byproduct liberated during the reaction (Scheme 114).\(^{164} \)

\[
\text{\( \beta \)}\text{-keto ester} + \text{NH}_2\text{NH}_2 + \text{ArCHO} \rightarrow \text{benzodiazepine derivative}
\]

Scheme 114.
A green and efficient one-pot three-component synthesis of 2,4-disubstituted-3 \( H \)-benzo[\( b \)][1,4]diazepines has been reported by Palimkar et al.\(^{165} \) The methodology initially involves the formation of ynones via coupling of a wide range of acid chlorides with terminal alkynes catalyzed by Pd(OAc)\(_2\) under copper, ligand and solvent-free conditions in just 10 min at rt followed by the Michael addition and cyclocondensation of \( o \)-phenylenediamines added \textit{in situ} using water as a solvent at reflux temperature (Scheme 115). In addition, the structure of the benzodiazepine was confirmed to be the diimino molecule and not the enamine by X-ray crystallographic analysis of the benzodiazepine. The methodology has been successful in achieving the twin green chemistry objectives of a solvent and ligand free operation and the use of water as a non-hazardous, inexpensive and readily available solvent in the sequential reaction steps performed \textit{in situ}, thus combining the features of both economic and environmental advantages.

\[ \text{R} \text{NH}_2 + \text{R}^1 \text{Cl} + \text{R}^2 \rightarrow \text{Pd(OAc)}_2, \text{Et}_3 \text{N, rt} \rightarrow \text{Pd} \rightarrow \text{OPD, H}_2 \text{O, 100 °C} \]

\textbf{Scheme 115.}

2,4-Di(hetero)aryl substituted 2,3-dihydro 1,5-benzodiazepines, oxazepines, and thiazepines were readily synthesized in a three component one-pot process initiated by a coupling-isomerization sequence of an electron poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with 2-amino, 2-hydroxy, or 2-mercapto anilines (Scheme 116).\(^{166} \)

\[ \text{XH} + \text{Ar}_1 - \text{Hal} + \text{HO} = \text{Ar}_2 \rightarrow \text{Pd-Cu, THF, Et}_3 \text{N} \rightarrow \text{Ar}_1 = \text{Electron deficient (hetero)aryl, Ar}_2 = \text{Aryl, X = NH, O, S} \]

\textbf{Scheme 116.}

Indole-fused benzo-1,4-diazepines were synthesized by copper-catalyzed domino three-component coupling-indole formation- N-arylation under microwave irradiation from a simple N-mesityl-2-ethynylaniline. This method was also applicable to the formation of heterocycle-fused 1,4-diazepines (Scheme 117).\(^{167} \)
1,3-Dianions are popular intermediates in many synthetic transformations.\textsuperscript{168} When 1- and 3-
positions are functionalized differently, such dianions have nucleophilic sites of different
reactivity. This makes them valuable for MCRs, since different electrophiles can be trapped in
sequential and regioselective manner, leading to complex reaction products that would otherwise
be difficult to prepare. Langer et al recently managed to synthesized medium size lactones by
multiple anion capture reactions of 1,3-dianions (Scheme 118).\textsuperscript{169}

```
Ph 1) KH
Ph 2) n-BuLi
```

**Scheme 118.**

Similar observations were made when dianions of 2-methylbenzimidazole were treated with one
equivalent of benzophenone and then with phthalic dichloride giving a nine membered
heterocycle in 19 % yield (Scheme 119).\textsuperscript{170}

```
N
N

```

**Scheme 119.**
1.7. Conclusion

Nitrogen, oxygen and sulphur containing heterocycles are common structural elements in many natural products and pharmacologically active substances. Accordingly, development of efficient methods for the synthesis of heterocyclic compounds has been challenging organic chemists for over a century. In the course of the time, MCRs have proved a convenient tool for the construction of many classes of heterocyclic compounds. In this review, heterocycles are categorized by the size of the ring and type as well as number of heteroatoms present in the ring. The methods that have been published so far for the synthesis of heterocycles are also categorized which provides some insight into logic of multi-component reaction in general. Many interesting examples have been put forward and it has become evident that almost all classes of heterocycles are now accessible by means of flexible multi-component procedures. As has been emphasized, MCRs are well appreciated tool for generation of moderate to large libraries of related heterocyclic compounds that are to be screened for pharmacological activity or ligands for novel transition metal catalysis. MCR chemistry with its tremendous advantages in terms of accessible chemical structure space, diversity and efficiency can help to achieve more rapidly technological and scientific advancements. With incredible foresight, Ivar Ugi recognized already in 1961 that MCR is ideally suited to probe structure-activity relationships via the synthesis of “large collections of compounds”, which nowadays are referred to as libraries. The labor efficiency and the access to such an enormous chemical structure space is a major driving force behind the recent flurry of activity in MCR research and patent applications. It has now become an interesting area of research in organic synthesis. It seems a safe prediction that the use of MCRs for the fast, efficient discovery and development of novel materials will dramatically increase in the near future.
1.8. References


Chapter 1
Multi-Component Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

111. Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; der Eycken, E. V. Org. Lett. 2004, 6, 4223.
122. Stevenson, P. J.; Graham, I. Arkivoc 2003, 139-144.