Chapter I

Introduction

Heterocyclic compounds are of fundamental importance to biological processes and are wide-spread as natural products. Synthetically produced heterocycles designed by organic chemists are as agrochemicals and pharmaceuticals and play an important role in human life. Many of the most famous natural alkaloids or unnatural drugs consist of one heterocycle [1].

In addition, these heterocycles are frequently substituted in a chiral fashion. The structural diversity of these heterocyclic motifs is enormous, since variation in ring size, number and nature of the heteroatom and substitution pattern on the rings is effectively unlimited. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. Heterocyclic derivatives such as morphine alkaloids, β-lactam antibiotics and benzodiazepines are just a few examples from various pharmaceuticals featuring a heterocyclic component [2].

However, the range of easily accessible and suitably functionalised heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. Therefore, the development of new, rapid and clean synthetic routes towards focused libraries of such compounds is of great importance to both medicinal and synthetic chemists [3]. Some of the representative examples are Efavirenz (1) a HIV-1 non-nucleoside reverse transcriptase inhibitor, Vinblastine (2) anti-cancer chemotherapeutic agent, Fenoldopam mesylate (3) a dopamine D1-like receptor.
Representative heterocyclic compounds:

(1)

Efavirenz, a HIV-1 non-nucleoside reverse transcriptase inhibitor

(2)

Vinblastine, anti-cancer chemotherapeutic agent
Fenoldopam mesylate, a dopamine D1-like receptor

Indoles are an important class of compounds that constitute the basic framework in number of alkaloids of biological significance such as dutadrupine (4), physostigmine (5), canthinone (6), ajmalicine (7). Indole nucleus occurs in several natural compounds and pharmacologically active substances displaying a broad range of biological activity. Indole derivatives have been found to possess antihypertensive and antipsychotic drugs. In addition, some indole derivatives have been shown to possess anticancer and antineoplastic properties.
Cycloaddition reactions are one of the most important classes of reaction in synthetic chemistry. The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five member nitrogen heterocycles[4,5]. Mechanistic investigation and synthetic application were established through the work of Rolf Huisgen [6]. Hence, the reaction is sometimes referred to as the Huisgen cycloaddition (this term is often used to specifically describe the 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate 1,2,3-triazole). The intramolecular alkyne–azide Huisgen [3+2] cycloaddition reaction as a ‘click-chemistry’ reaction without a metal catalyst has been studied under neutral conditions.
Several new developments in the field of medicinal chemistry are associated with quinolines. Quinoline nucleus occurs in several natural compounds like Cinchona Alkaloids and pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess antimicrobial [7], antituberculosis [8], cytotoxicity [9], anticonvulsant [10], and anti-inflammatory [11] agents. Some of the quinoline derivatives such as dutadrupine, mepacrine and levofloxacin are in clinical use.

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases.

The bark of Cinchona plant (also known as Jesuit’s or Cardinal’s bark) containing quinine was utilized to treat palpitations [12], fevers and tertians since more than 200 years ago. Quinidine, a diastereoisomer of quinine was in the early 20th century acknowledged as the most potent of the antiarrhythmic compounds isolated from the Cinchona plant [13].

Compounds containing quinoline moieties are most widely used as antimalarials [14], antibacterials [15], antifungals [16] and anticancer agents [17]. Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents [18]. They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes.

Furthermore, these compounds find applications in chemistry of transition metal catalyst for uniform polymerization and luminescence chemistry [19]. Quinoline derivatives also act as antifoaming agent in refineries [20]. Owing to such significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry.
The first formal synthesis was reported by Skraup over a century ago [21]. It involved treatment of aniline with acrolein under heated sulfuric acid but later several variations to the original Skraup synthesis have been reported [22]. In such sequence of study, it has been seen that the activity of such nucleus may be due to the presence of fused pyridine. Placing the ylide dipole and the alkene within the same molecule provides direct access to bicyclic or polycyclic product of considerable complexity.

The dipolar cycloaddition reaction of azomethine ylides is one of the most important methods for the formation of pyrrolidines and pyrroles. By conducting the reaction in an intramolecular sense, one can produce two rings and up to four new chiral centres, making it a powerful method for organic synthesis.

The intramolecular dipolar cycloaddition reaction of azomethine ylides has progressed significantly since the first report nearly 30 years ago. The reaction has found use for the synthesis of a number of natural products of core ring systems and of potential medicinal compounds. The reaction is amenable to the solid phase and has allowed the production of libraries of compounds.

A number of different methods exist for the formation of the azomethine ylide and hence a variety of functional groups can be installed in the bicyclic or polycyclic product.

In general anion-stabilizing group (often a carbonyl group) is used to help formation of the ylide and there is scope for further development of methods that allow the formation of the non stabilized ylides. The reaction is often successful with unactivated alkenes or alkynes and this is one of the advantages of this chemistry. As a result of the variety of substitution patterns and good yields, the reaction is likely to continue to attract widespread interest and use in synthetic organic chemistry.
These cycloaddition reactions performed by reacting α-amino acids and carbonyl compounds gave rise to in situ azomethine-ylide formation which leads to formation of the heterocyclic ring. Within this class, the 1,3-dipolar cycloaddition reaction has found extensive use as a high-yielding and beneficial method for the synthesis of many different heterocyclic compounds [23, 24].

A main issue in modern synthetic organic chemistry which deals with the preparation of natural products, pharmaceuticals, agrochemicals and other important materials is the improvement of efficiency, the avoidance of toxic reagents, the reduction of waste and the responsible treatment of our resources. It is hoped that this work would be a useful resource in the interesting field of cycloaddition reactions and will inspire further developments in this area.

It was in 1963 that Huisgen laid out the classification of 1,3-dipoles and the concepts for the 1,3-dipolar cycloaddition reactions although it was not until 1976 that the first intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylide was reported. Since then impressive developments have been described in this area with the establishment of various useful methods for the formation of azomethine ylides and the determination of the requirements for a successful intramolecular cycloaddition reaction.

Quinoline nucleus occurs in several natural compounds displaying a broad range of biological and pharmacological activity. The utility of quinoline derivatives in the areas of medicine, food, catalyst, dye, materials, refineries and electronics is well established. As a result, the synthesis of quinoline core and its derivatives have been an attractive goal for the synthetic organic chemist. Synthesis of 2-chloro-3-formyl quinolines has received a greater attention due to the presence of biologically active quinoline nucleus.
Indole is a heterocyclic scaffold of paramount importance to human race. In the recent past, there have been several new developments in the chemistry associated with the indoles. Importance of Indolino-Pyrrolidine compounds in pharmaceutical industries is unequivocal.

A systematic study of Indolino-Pyrrolidines is warranted for it may lead to in-depth understanding of concepts and problems on molecular structure, spectral characteristics and biochemical reactivity.

Triazoles are important five membered heterocyclic compounds which show various medicinal properties such as hypoglycaemic activity, antimicrobial [25], anti-inflammatory [26], anticonvulsant [27], antimalarial [28] and antineoplastic activity [29]. Substituted 1,2,4, triazoles find many useful applications as analytical reagents for determination of boron [30], antimony [31] and cobalt [32]. Other triazoles find many synthetic uses as halogenating agents or as activating polymeric reagents [33]. Now 1,2,3-triazoles derivatives are widely used as biocides and as antifungal agents.

Extensive research is going on in using triazoles as OLED receptors drawing great attention by scientists all over the world as it has many opportunities for application development. Thus a detailed research in this field may lead to intellectuality stimulating and commercially rewarding results.

Indolizidine and pyrrolizilidine alkaloids are naturally occurring N-heterocyclic metabolites which include a large number of compounds that display pronounced biological and pharmacological activities with therapeutic potential. Stellettamide A, a recently discovered indazolidine alkaloid, has shown antifungal activity and cytotoxicity against epithelium cells. D. A. Barr et al [34] has synthesized some of the cycloadducts (10) through inter and intra-molecular cycloaddition of olefins (8) with phenylglycine, alanine and glycine esters (9) to a range of dipolarophiles via metallo-1,3-dipole formation at room temperature. Silver acetate was used as a catalyst and the reaction was carried out in acetonitrile.
M. Joucla et al [35] has prepared some of the cycloadducts (13) by reacting benzaldehyde (11), alpha-aminoester (12) and alkenes in refluxing toluene for several hours and driving out the water by means of Dean-Stark trap. After removal of the solvent under vacuum, they were able to obtain the pyrrolidines in quantitative yields.

M. Potacek et al [36] has synthesized hexahydrochromeno [4,3-b] pyrrolidines (17) by the cycloaddition reaction between aldehyde (14) and amine (15). These particular reagents were previously studied under the classical reaction conditions (various solvents, classical heating, various catalysts) and microwave heating using toluene as a solvent, but low yields. After changing various conditions, they found out that the presence of less electron-withdrawing groups on the dipole should lead to the higher reaction yields via the intermediate (16), even though the acidity of the hydrogen atom next to electron-withdrawing group is lower compared to ester stabilized 1,3-dipole.
The reaction of cyano-stabilized dipole gave as expected, desired cycloadducts even at prolonged time only in low yield.

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\begin{align*}
\text{(14)} & \quad + \quad \text{(15)} \\
\xrightarrow{\text{microwave}} & \quad \text{(16)} \\
\end{align*}
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S. Kathiravan et al [37] has synthesised a variety of polycyclic heterocycles (20) by 1,3-dipolar cyclo-addition using Baylis-Hillman adduct derivatives (18) as dipolarophiles with pyrrole-2-carbaldehyde (19).
Recently S. Kathiravan et al [38] has synthesised novel heterocycles through cycloaddition reaction. They reported that it is an expeditious and facile protocol for the synthesis of novel napthopyrano pyrrolidizines (23) and Indolizidine by Intramolecular 1,3-dipolar cycloaddition of azomethine ylides generated from napthaldehyde (22) prepared from Baylis-Hillman adducts (21) in a one-pot reaction.

![Chemical Structures]

Novel regio and stereoselective 3-spiro-pyrrolidines (26) from nitroolefines were prepared by M. Bakthadoss et al [39]. They have selected (E)-2-nitro-3-phenylprop-2-en-1-ol (24), a Baylis-Hillman adduct derived from nitrostyrene, as a starting material for [3+2] cycloaddition reaction with dipoles generated from sarcosine with isatin (25). Best results were obtained when (24) was treated with isatin and L-proline without any catalyst in acetonitrile as solvent.
H. Menasara et al [40] has prepared some new 3-pyrrolidinylquinolines (29) by 1,3-dipolar cycloaddition of a symmetrical, unstablized azomethine ylide to the corresponding $\alpha,\beta$-unsaturated esters (27) to give pyrrole derivative (28). Oxidative dehydrogenation of these cycloadducts with active MnO$_2$ under mild condition provided the corresponding pyrroles.

In addition to the 1,3 dipolar cycloaddition reaction, our interest extends to the synthesis of pyrano pyridones through one-pot multicomponent synthesis. Igor. V. Magedov et al [41] has prepared some pyrano[3,2-c]pyridones (33) through one-step multicomponent synthesis by the reaction of pyridone (30) with aryl aldehydes (31) and malononitrile (32) in refluxing ethanol to yield pyrano pyridones.
REFERENCES


