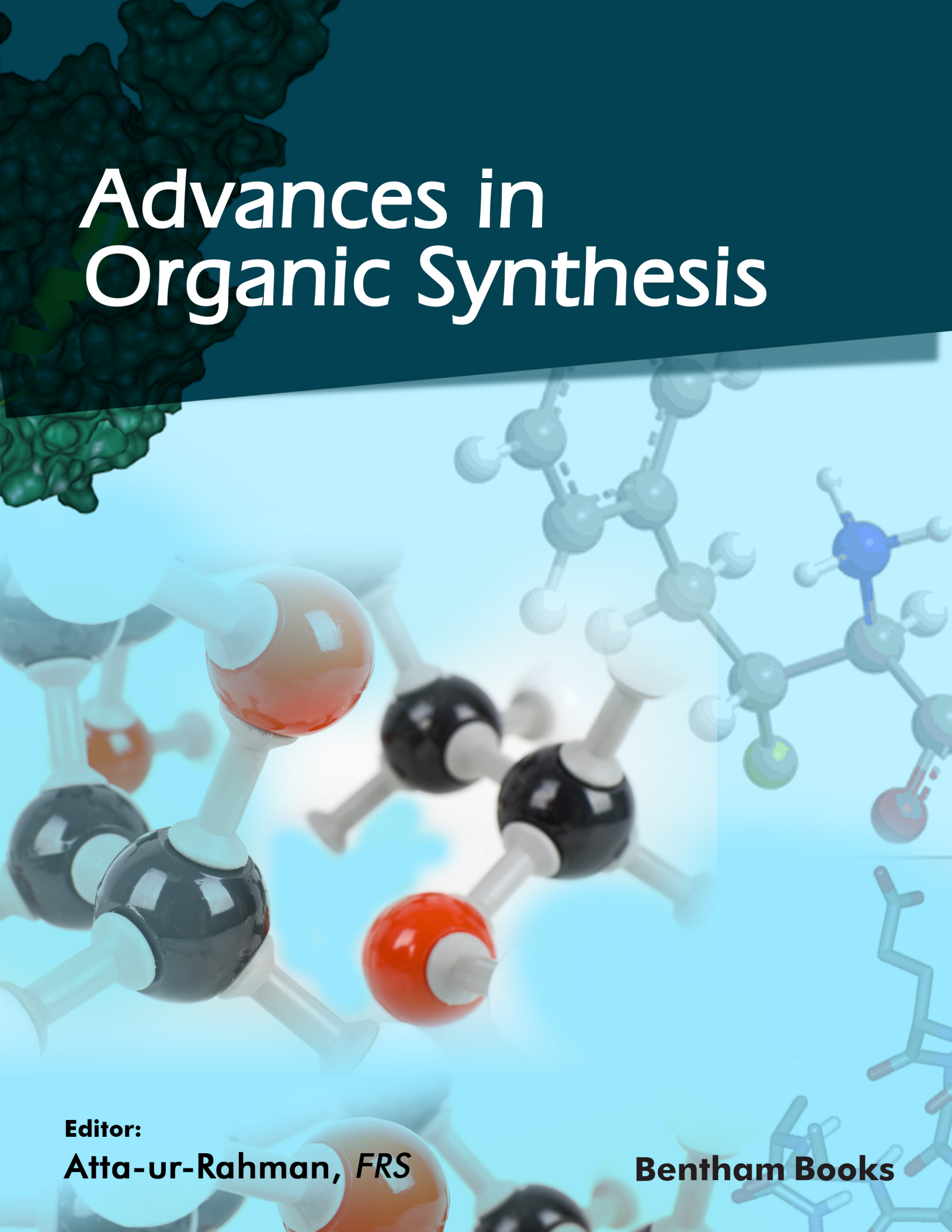
Advances in Organic Synthesis



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PREFACE

The 17th volume of *Advances in Organic Synthesis* presents recent exciting developments in synthetic organic chemistry. The chapters are written by eminent researchers in the field. The topics include multicomponent synthesis of heterocycles by microwave irradiation, stereoselective procedures for the synthesis of olefins, advanced microwave-assisted organic synthetic method in organic chemistry, synthesis of five and six-membered N-heterocycle rings from diaminomaleonitrile, current and future perspectives of peptidomimetics on HIV protease inhibitors, and methods to synthesize benzothiazines and their derivatives.

This volume should prove to be a valuable resource for organic chemists, pharmaceutical scientists and postgraduate students seeking updated and critically important information on recent important developments in synthetic organic chemistry. I hope that the readers will find these reviews valuable and thought-provoking, and that trigger further research in the quest for new developments in the field.

I am thankful to the efficient team of Bentham Science Publishers for the timely efforts, especially the editorial personnel Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (Incharge eBooks Department), and Ms. Asma Ahmed (Manager Publications).

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CHAPTER 1

Multicomponent Synthesis of Heterocycles by Microwave Irradiation

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Abstract: The multicomponent reactions (MCRs) are vital for producing structurally varied molecular objects. Multicomponent reactions (MCRs) contain three or more synthetic stages and are carried out without isolation of any intermediate, thus requiring mild reaction conditions. They are eco-friendly and cost-effective, have a short reaction time, produce higher yields, and require raw materials. The use of microwave irradiation in green organic synthesis sustains some of the aims of "green and sustainable chemistry." It offers several benefits over the conventional approach in reducing time, reaction rates, selectivity, product yields, *etc*. Consequently, the preparation of various heterocycles using a one-pot multicomponent method combined with the application of microwave irradiation is one of the best areas amongst synthetic chemistry. The present study illustrates an overview of recent progress on microwave-irradiated, one-pot multicomponent synthesis of heterocycles.

Keywords: Benzoxazoles, Conventional Heating, Furans, Fused Heterocycles, Green Chemistry, Heating Mechanism, Heterocyclic Compounds, Imidazoles, Multicomponent Synthesis, Microwave Effects, Microwave Irradiation, One-pot Reaction, Pyrans, Pyridines, Pyrimidines, Pyrroles, Reaction selectivity, Spiro-heterocycles, Thiazoles, Triazoles.

INTRODUCTION

The proper utility of time is undoubtedly applicable for chemical science principally in organic synthetic transformations, as much as in other areas of life [1]. Customarily, to optimize an existing or establish a novel synthetic route for sustainability consideration, product purity, and yield, many time-consuming and trial-error experiments are required [2, 3].

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Any evolved method that conserves time would enable chemists to administer new processes and make theories faster, and there will be additional time to promote scientific innovation. Hence this gives rise to the need for the application of microwave chemistry [4]. It serves the potential of being a rapid synthetic technique.

Nowadays, researchers in both industries and academia face the challenges of developing environmentally benign protocols to design new molecules [5]. Waste prevention, safe solvent, energy efficiency, and atom economy are among the 12 green chemistry principles related to synthetic chemistry [6 - 8]. The microwave energy utilization is beneficial in terms of depreciated energy needed for reactions, selective heating, and adjustability with green or non-toxic solvents (*e.g.*, water, ethanol, *etc*.) [9]. The microwave tool gets amalgamated with the above-mentioned green chemistry principles to make it attractive to organic synthesis [10].

MICROWAVE CHEMISTRY

Origin

Previously, the robust interactivity of microwave irradiation by materials was inadvertently uncovered in 1945 by Percy LeBaron Spencer [11]. He noticed a candy bar that melted in his pocket; this happened while working on microwaves' radar application [12]. The first commercial microwave oven was developed at the Raytheon Company in 1952 by Spencer and other co-workers. In the 1960s, microwave irradiation was used as a temperature jumper, but its application in chemistry was reported in the 1970s in the decomposition of ethers, alcohols, and ketones [6]. In 1986, great attention was given to reactions conducted under microwaves after perceiving the accelerated rates in microwave ovens [6 - 8]. Eventually, the microwave tool has converted into an asset in synthetic chemistry [13]. However, few areas in organic chemistry have not employed microwave technology to improve various chemical reactions [14]. Microwave procedure has also been exploited as an influential tool in other areas of synthetic chemistry, like catalysis [15, 16], green chemistry [17], polymer chemistry [18], combinational and medicinal chemistry [18 - 20], heterocyclic chemistry [21], nanotechnology [22], material sciences [23], and peptide synthesis [24]. This section discusses the principles of microwave irradiation (microwave effects and dielectric heating), compares it to classical methods, and reviews the merits and limitations of using a microwave tool. Additionally, we have exploited the microwave technology to obtain the desired selectivity and showcase microwave-enhanced organic reactions.

Microwave Devices

Formerly organic syntheses using microwave irradiation reported in the late 1990s were carried out using domestic microwave ovens. A domestic microwave oven uses pulsed irradiation (on-off cycles of the magnetron), in which monitoring and controlling temperature and pressure (safety issues) are quite difficult. Now, the industrial microwave reactors are equipped with a built-in magnetic stirrer as well as temperature monitors (fiber optic probes or IR sensors) and pressure controls. In most cases, temperature and pressure can be operated by software that controls the reactor's power input. Currently, there are two different design approaches to microwave reactors; multimode (Fig. **1a**) and monomode reactors (Fig. **1b**). In a multimode microwave (as in household microwave ovens), the microwaves enter the cavity and are reflected by the walls. The microwaves are uniformly distributed throughout a large volume using a mode stirrer. In a monomode reactor, which has a much smaller cavity, the electromagnetic irradiation is focused straight into the reaction vessel. The microwaves are generated as standing waves on account of the geometry and the location of the cavity from the radiation source. Each microwave instrument has its own advantages and drawbacks. The multimode microwave unit can accommodate any size of glassware (sometimes a few at a time), but reaction productivity decreases because the irradiation is spread "all over" the microwave. In the monomode microwave, the irradiation is focused on one small vessel, hence more efficient. Microwave reactions can be carried out in sealed vessels under pressure (sealed vessel mode) or unsealed vessels at atmospheric pressure (open vessel mode). An open vessel reactor often is sealed with a cap to maintain an inert atmosphere. Modern monomode reactors are designed for straightforward monitoring of closed vessel reactions.

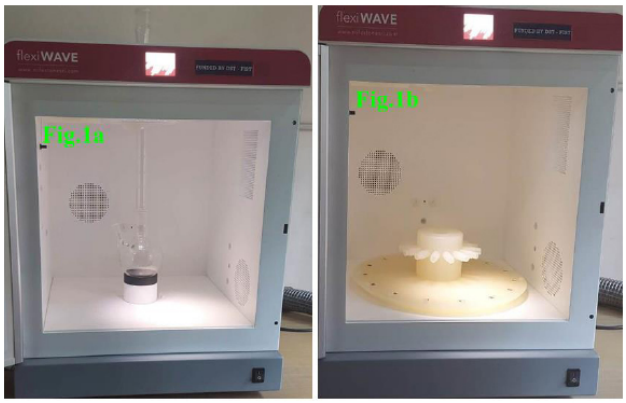

Fig. (1). The MWI devices **(a)** the monomode reactor MW **(b)** the multimode reactor MW.

CHAPTER 2

Stereoselective Procedures for the Synthesis of Olefines

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Abstract: Olefins are molecules containing double bonds and are an active functional class. They have the potential to react easily due to the pi bonds in their structures. Therefore, olefins themselves form a biologically active class. In addition, they are pioneer molecules in obtaining different derivatives over many reaction types in organic chemistry. The presence of double bonds brings along geometric isomers (*e.g.*, *cis, trans, E, Z*). The biological activities of olefins differ in geometric isomers. Therefore, stereoselectivity is important for the synthesis of olefins. In stereoselective olefin synthesis, the control is in the hands of the synthetic organic chemist. Stereoselectivity can be controlled with a correct and practical method. In this study, i) geometric isomers ii) biological activities and iii) stereoselective synthesis of olefins are focused.

Keywords: Biological Activity, Geometric Isomer, Olefin, Stereoselective Synthesis.

INTRODUCTION

Isomerism in Alkenes

Atoms come together to form bonds and molecules are formed. As it is known, the first bond formed between the atoms is the sigma bond and the second bond is the pi bond. The sigma bond is formed by the head-to-head overlap of atomic or hybrid orbitals on the line connecting the nuclei of atoms. The pi bond occurs when the p orbitals interact side by side. For this reason, while the sigma bond is a strong bond, the pi bond is a weaker bond, and it can be claimed that pi bonds will break first if bond breakage occurs in multiple bonds. Since the sigma bond is a single bond, it is possible for the bond and the atoms bound by the sigma bond to rotate around itself. However, the presence of the pi bond gives the molecule a

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barrier to rotation. Geometric isomers are observed in molecules with rotation barriers (Fig. **1**) [1 - 5].

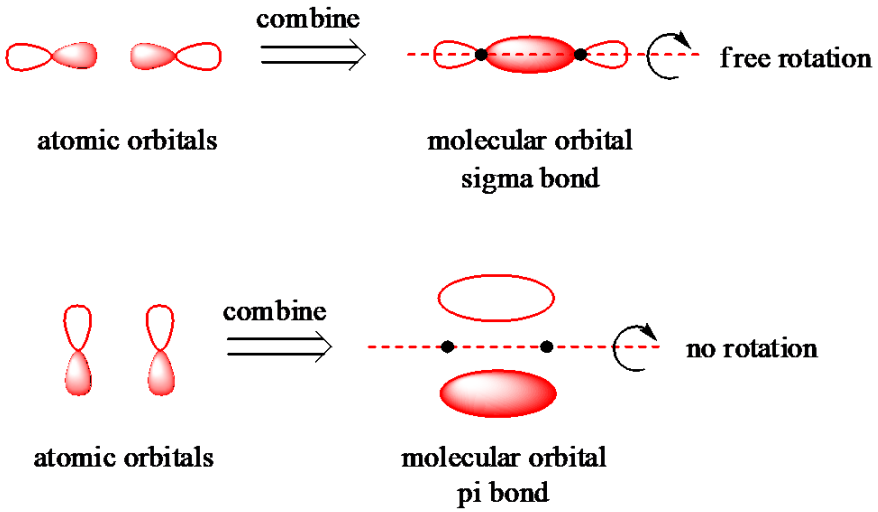

Fig. (1). Sigma and pi bond formation.

The geometric isomerism observed in olefins determines their usage areas. In geometric isomers, along with the different physical properties, both their biological activities and reaction potentials differ.

For example, two different products emerge with the polymerization reaction observed through the 1,4-addition of isoprene [6]. These products are geometric isomers of each other. However, their physical properties are completely different from each other. One of these products is poly (*trans*-1,4-isoprene) [7] and it has a symmetrical structure. This product does not show elasticity since it can be crystallized easily and is fragile. However, poly (cis-1,4-isoprene) [8], which is the other polymerization product, is known as natural rubber. This product is soft and sticky at room temperature. The natural rubber with elastomer properties is also called latex (Fig. **2**).

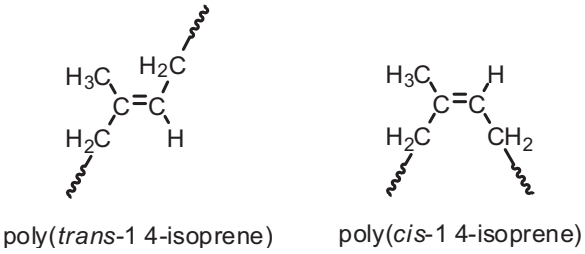

Fig. (2). Geometric isomer in polymers.

The *cis* and *trans* isomer of the SNN clamp ligand reacted with K_2PdCl_4 to obtain palladium (II) complexes. Both complexes showed different activity against breast cancer cell lines. In addition, these complexes generally have low toxicity and high activity (Fig. **3**) [9].

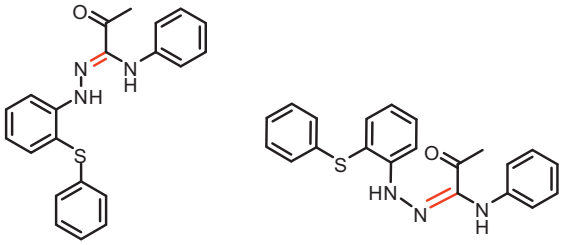

Fig. (3). Geometric isomers effective in cancer cells.

The epoxidation of a *cis* and a *trans* alkene with meta chlorine perbenzoic acid (m-CPBA) is a diastereoselective reaction. While a single product is observed with an attack from the surface where the steric effect is low in *cis* alkene, the product mixture is observed attacking both surfaces in *trans* alkene. It can be seen from this example that the reaction of geometric isomers to the same reagent is different (Fig. **4**) [10].

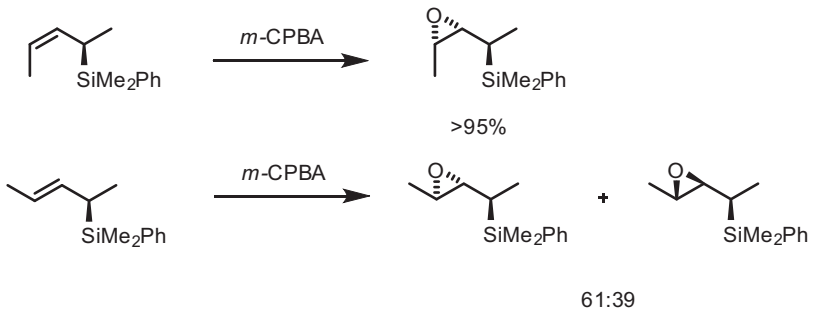

Fig. (4). The epoxidation of geometric isomers.

We tried to explain the physical, biological and chemical effects of geometric isomers. Let's take a brief look at the nomenclature of geomeric isomers.

Cis v/s Trans Nomenclature

In order to mention geometric isomers in alkenes, there must be disubstituted alkenes. In other words, different groups must be attached to each carbon atom bonded to the double bond. However, in this case, geometric isomerism arises and *cis/trans* nomenclature can be made (Fig. **5**).

CHAPTER 3

Advanced Microwave Assisted Organic Synthesis Method in Organic Chemistry

Manish Srivastava[*, 1], **Anjali Banger**[1], **Ravina Yadav**[2], **Anamika Srivastava**[1], **Jaya Dwivedi**[1] and **Varun Rawat**[*, 3]

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Abstract: This chapter presents an outline of chemical reactions performed while utilizing microwave irradiation. The improvement in economic strategies has taken cognizance and acknowledgment of environment-friendly and cost-effective procedures having the most negligible impact on the environment. Compared to other methods, microwave-assisted methods proved to be more favorable substitutes for conventional laboratory heating systems; many chemical reactions have been accomplished, refining prevailing procedures with practical conclusions than the reactions proceeded under the conventional heating system. Reactions executed *via* catalysis in an aqueous medium enhanced the eco-friendly procedures, and the reactions executed *via* catalysis in fluid medium enhanced environmental conventions. In this chapter, we will discuss microwave-assisted catalytic approaches, which have been used for the preparation of various heterocyclic compounds, preparation of peptides, urea and coordination polymers having carboxyl group, and various other chemical reactions. The focus of this work is to highlight the recent advances in the field of Microwave-assisted organic reactions like oxidation, reduction, coupling, functionalization, heterocyclic compounds synthesis, multi-component reactions, and nucleophilic substitutions in water.

Keywords: Microwave irradiation, Microwave-assisted synthesis, Green chemistry.

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INTRODUCTION

Microwaves are defined as electromagnetic waves with vacuum wavelengths ranging in between 0.1 to 100 cm or, equivalently, with frequencies between 0.3-300 GHz. Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions [1]. Microwave irradiation tends to produce reaction accelerations as a consequence of the specific heating rate which cannot be reproduced by classical heating [2]. For many organic syntheses involving extended reaction times (over 30 min), microwave-assisted organic synthesis (MAOS) has become increasingly popular by shortening that reaction time, increasing the yield [3]. Microwave-accelerated preparation of organic compounds has been established as a new "lead" in organic synthesis. Microwave (MW) assisted preparation of organic compounds has synthesized influential and sustainable tools in synthetic chemistry and has fascinated the keen interest of scientists because of its particular highlights together with the proficient atomic application, reaction homogeneousness, and probable adjustment of activation constraints. From the past ten years, due to significant advancement in green chemistry, it counts in major scientific principles. Microwave-assisted preparation of organic compounds has enhanced in recent years and is considered much better as compared to conventional heating. One of the foremost emerging areas is the green synthesis necessary for sustainable industrial processes [4]. Its analysis and applications emphasized on improvement of clean and gentle chemically assisted procedures, with varied unused innovations being established every year [5]. Recently, MW-assisted chemistry has become a very helpful practice for varied applications in the preparation of organic compounds and their transformation [6, 7]. The technique offers basic, quick, efficient, clean, and economical preparation of varied organic compounds. Significant advantages of this innovation comprise of extremely accelerated reaction rate, less reaction time with enhancement in yield and quantity of product. Recently, this procedure has been considered a vital approach towards green chemistry, since it is eco-friendly. The wide opportunities also include definite synthesis design [8], renewable feedstock usage through the translation of biomass to chemically synthesized raw materials [9, 10], nontoxic solvents preparation [11, 12], biocatalytic applications [13, 14], and the improvement of innovative objectives for progression estimation [15].

Microwave has been connected completely to areas and forms like waste treatment, drying, heating, *etc*., in comparison to conventional heating systems like heating *via* the use of oil bath. Heating practices performed under optimum temperature through microwave have proved to be valuable innovation in reducing the time taken by the reaction. Microwave-assisted reactions are more advantageous than conventional heating because of their short reaction time and

cleaner products [16]. Microwave technology is useful in the assemblage of preferred bioactive molecules along with the formation of a simple particle. The choice of a suitable solvent, reagent, and catalyst directly emphasizes better economically efficient, green, and sustainable results since it will minimize the waste generated by the chemicals and help in making the environment more reliable [17]. In this case, a reasonable choice of solvent appears to be the most significant choice. Organic solvent may be by environmentally friendly solvents like water [18, 19]. In the conventional method, conductive heating is preferred for preparation *via* the use of external heat elements like oil baths resulting in poor energy exchange. While microwave-assisted technique uses coordinate coupling criteria for producing heat *via* the use of reaction mixture which comprises of various solvents. To minimize the adverse effect caused by cooling and heating, there is a need for some effective and easy methods that will utilize a different type of energy source such as microwave irradiation to simplify chemically-driven reactions. It has gained a lot of popularity in its concerned scientific area [20, 21]. Microwave irradiation has been used to provide energy for the growth of MOFs. Microwave-assisted synthesis is based on the interaction between electromagnetic waves and mobile electric charges, such as polar solvent molecules or ions in the solution. The advantages of this method include high efficiency, phase selectivity, particle size reduction, and morphology control [22]. The technology is gaining widespread acceptance in drug discovery research. Microwave-assisted synthesis, in general, is likely to have a large impact on medicinal/organic chemistry communities. Compared to the traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time and this is ideally suited for combinatorial chemistry in drug discovery to produce a large number of compounds [23]. A recent study compared the productivity of preparation by conventional method and microwave-assisted method has been demonstrated which concluded that for most chemical changes, a significant energy saving could be anticipated utilizing microwaves as the source of energy on research facility scale [24]. The microwave-assisted chemical reactions envelop the preparation of organic, coordination, organometallic, ceramic, solid-state materials, *etc*. Few microwave-assisted reactions which were performed earlier include the Ene reaction, Mannich reaction, Suzuki reaction, Diels-Alder reaction, dehydration, esterification, epoxidation, condensations, reductions, hydrolysis, *etc*. Due to the poor solubility, organic solvents still prevail natural solvents like water are still, and it can also be concluded that sometimes they are completely insoluble in an aqueous medium [25]. The combination of microwave-assisted organic reactions (MAOs) and water has gained attention as a green process in comparison to the sluggish conventional heating system [26]. Water has gained much attention from both economic, and natural characteristics [27]. The interaction between the polar substances and the electromagnetic

CHAPTER 4

Five and Six-membered N-heterocycle Rings from Diaminomaleonitrile

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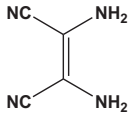
Abstract: Diaminomaleonitrile (DAMN) is a tetramer of hydrogen cyanide that has been used as the source of purine bases such as adenine. In the literature, DAMN seems to be an essential element used to synthesize various N-heterocyclic compounds. Numerous pharmaceutical and industrial applications have been described for DAMN-derived compounds. Among these compounds are five and six-membered N-heterocyclic rings, and since their emergence, DAMN has been extensively investigated as an inexpensive and readily available reagent in synthetic and complex chemistry applications, including those that produce dyes and pigments. As a rich nitrogen source, DAMN occupies an important position in synthetic heterocyclic chemistry. Various synthetic methodologies and diverse heterocyclic structures have been produced and approved across a broad array of industrial fields. This chapter covers five and six-membered rings obtained directly from DAMN.

Keywords: Antimicrobial, Antitumour, Cyclization, Diaminomaleonitrile, Hydrogen cyanide, Imidazole, Medicinal chemistry, N-heterocycles, Pharmaceuticals, Pyrazine, Pyrimidine, Triazole.

INTRODUCTION

In recent decades, diaminomaleonitrile (DAMN) **1**—a tetramer produced from HCN polymerization [1, 2] has emerged to receive increased consideration as a versatile building block in a diversity of biological molecules (*e.g.*, nucleotides). Additionally, it has been broadly used to synthesize a wide range of N-heterocycles [3, 4] (Scheme. **1**).



DAMN

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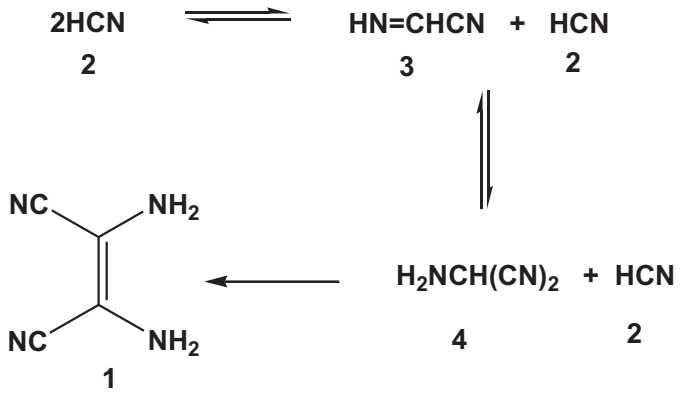


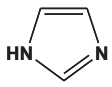
Scheme. (1). Synthesis of DAMN **1** from HCN.

Some studies suggest that DAMN **1** could be the origin of purine bases vital to the evolution of life on earth [1 - 9]. Therefore, the search for simple and feasible routes to nitrogen-containing compounds with potential applications in pharmaceuticals and industry remains energetic [3, 4]. Indeed, interest in DAMN **1** and its derivatives has elevated worldwide, given DAMN's essential role in synthetic heterocyclic chemistry. The importance of DAMN **1** in recent years has increased following several reviews that describe its use as a building block to synthesize various nitrogen-containing compounds, in addition to indispensable intermediates that facilitate further chemical transformations. Motivated by this, several successful conversions have led to various noteworthy products; especially, researchers have produced and reported on five and six-membered rings. DAMN **1** has been extensively used to generate valuable and good-quality compounds found to be effective in numerous industries, but chiefly the drug industry.

SYNTHESIS OF FIVE-MEMBERED RINGS

Synthesis of Imidazoles

Imidazoles **5** are captivating nitrogen-containing heterocyclic compounds. They constitute a part of several important biological molecules, including the amino acid histidine, cobalamin (vitamin B12), biotin (vitamin H), histamine, purines, and the DNA base component structure [10 - 12].



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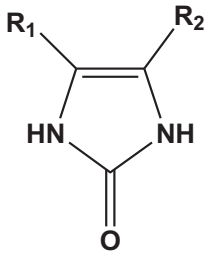
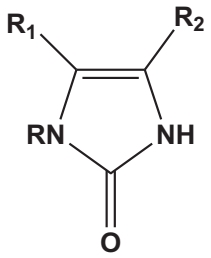
Over the last century, the crucial role of imidazoles in numerous versatile applications (most notably pharmaceuticals) has widened the search for their synthesis [13 - 15]. They are the main unit in many approved drugs, including those that are anticancer [16], antibacterial [17], enzyme-inhibiting [18], antifungal [19], antiparasitic [20], and anti-inflammatory [21]. Therefore, one of the starting materials most frequently used to synthesize imidazoles is DAMN **1**, which is advantageous because it is an amenable and rich source of nitrogen that is both economical and readily available. It is noteworthy that DAMN **1** is one of the primary compounds used to generate a group of N-heterocycles, including imidazoles.

The reaction of phosgene [3, 4, 22] or chloroformates [3, 4, 23] with DAMN **1** generates imidazole **6**, while imidazoles **7** and **8** are formed when DAMN **1** is made to react with CO_2 or Schiff base (R = NHR) under basic conditions, respectively [3, 4, 24, 25].

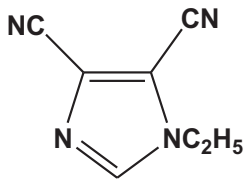




6 $R_1 = R_2 = CN$
7 $R_1 = CN$, $R_2 = CONH_2$

8 $R_1 = NH_2$, $R_2 = CONH_2$

In 1991, Johnson reported that 1-ethyl-4,5-dicyanoimidazole **9** can be obtained in an approximately 97% yield when DAMN **1** is heated to 102 °C with triethyl orthoformate in a 1:3 molar ratio for 4 h [26].



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In that study, Johnson produced 1,2-dimethylimidazole **10** as a minor product when DAMN **1** reacted with neat triethyl orthoacetate [26].

CHAPTER 5

Peptidomimetics: Current and Future Perspectives on HIV Protease Inhibitors

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Abstract: The peptidomimetic-based design and synthesis of HIV-1 protease and other entry inhibitors are generally oriented to block the viral receptor functionalities in the host cells. Most of the drugs classified under HIV-1 protease inhibitors are primarily optimized through substrate-based design strategies. The peptidomimetic drugs present in the market are non-hydrolyzable by the catalytic aspartic acid residues, an indispensable approach still used in designing potential pharmacophores for protease inhibitors. Thus, a variety of amino acid-containing hybrid small molecules are tested against the HIV-1 protease enzyme by incorporating essential fragments required to block protease functionalities. However, the appearance of mutations in HIV polyproteins is a key parameter to be seriously considered while designing peptidomimetics. Hence, comprehensive knowledge regarding HIV peptidomimetic/medicinal chemistry along with optimization strategy and organic synthesis awareness is critical in the current scenario. The present chapter is aimed to provide in-depth literature on medicinally optimized HIV-1 protease inhibitors, Tat-TAR RNA blockers with their synthesis, and later it is expanded to the peptidomimetics (entry inhibitors) involved in the envelope glycoprotein (gp120/gp41) and capsid inhibitors. Furthermore, the knowledge-based classification of HIV-1 protease inhibitors, anti-dimer agents, Tat-TAR RNA blockers, and entry inhibitors, along with their synthetic procedures, would serve as a single model template for scientific as well as academic research towards the development of anti-HIV peptidomimetics.

Keywords: Amino acids, ART, Capsid, Design, Drugs, Glycoprotein, HIV protease, Inhibitors, Identification, Optimization, Peptidomimetics, Peptoid, Peptide coupling, Transition state, Synthesis.

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INTRODUCTION TO HIV GENOME

The human immunodeficiency virus (HIV) belonging to the family *Lentivirus*, categorised as retrovirus, is divided into two types (HIV-1 and HIV-2), consisting of minor structural differences in their genome [1]. A typical HIV-1 RNA virus, with a size of around 9.7 kilobases, is more prevalent in HIV infections. The genomic sequence of HIV shows two different long terminal repeats (5'LTR and 3'LTR) encoded with polyproteins (Gag, Pol, and Env), accessory proteins (Vif, Vpr, Vpu, and Nef), regulatory components (Rev and Tat), and polyadenylation sites required for transcription [2]. The schematic representations of HIV-1 and HIV-2 genomes are provided in Fig. (**1**) labelled with essential polyproteins.

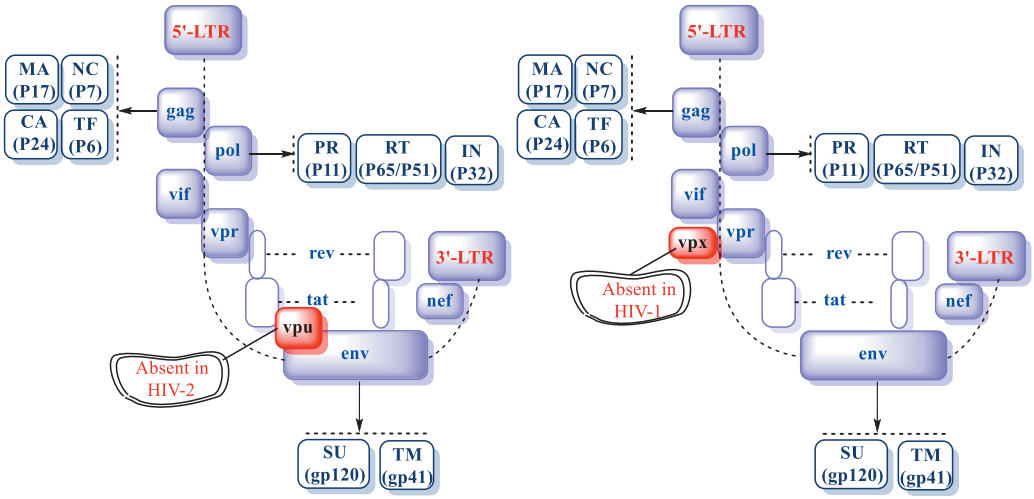

Fig. (1). HIV-1 and HIV-2 genomes labelled with essential polyproteins.

The primary Gag region of the genome undergoes cleavage by protease enzyme and is processed into Matrix (MA-P17), Nucleocapsid (NC-P7), Capsid domain (CA-P24), and trans-frame (TF-P6) proteins [3]. The matrix protein smears on the exterior surface of virus particles and is involved in RNA processing and assembly of virus along with glycoproteins (Env). The capsid protein is required to make the covering of the viral RNA genome in matured virus particles. It also functions as a precursor for Gag-Pol activity in the virions at the stage of viral assembly and plays a vital role in the post-entry stages [4]. The nucleocapsid is critical in the encapsulation of processed viral RNA, assembly, and reverse transcription stages, whereas the trans-frame protein is needed for composing viral particles with the Vpr region to initiate virus budding in the host cell membranes. The 3D structures of the Gag region are depicted in Fig. (**2**).

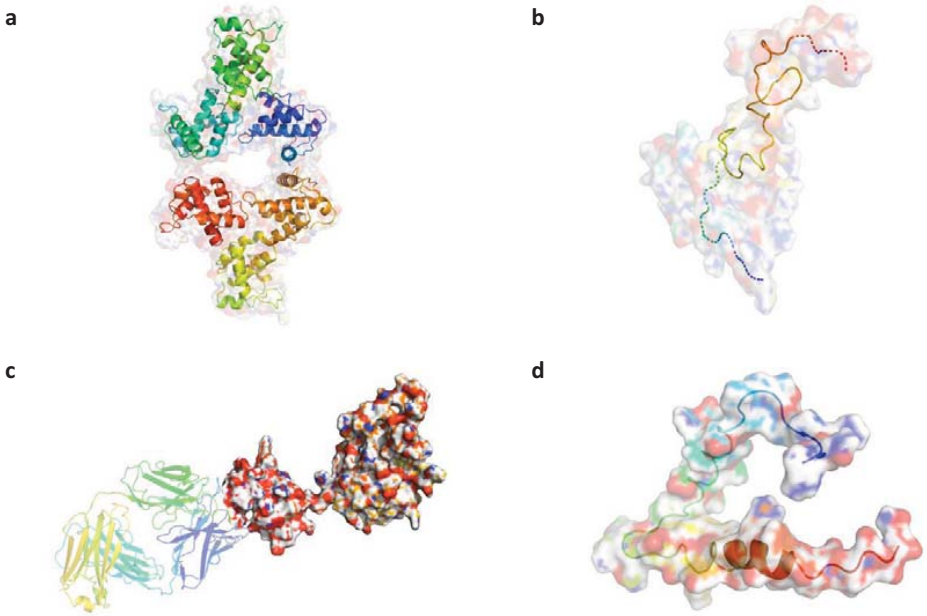

Fig. (2). 3D structures of HIV-1 Gag region; a) The 3D structures of matrix protein (P17), b) nucleocapsid (P7), c) capsid (P24) (surface) complexed with immunoglobulin, and d) trans frame protein (P6).

The Pal protein region also breaks into PR-protease (PR), RT-reverse transcriptase, and IN-integrase during cleavage of the Gag section by protease enzyme. The protease enzyme is considered a significant factor in determining virus infectivity [5]. The reverse transcriptase enzyme is a heterodimer template that handles the transcription of viral RNA into the pro-viral DNA before integration with host DNA. It also acts as DNA-directed DNA polymerase, RNA-directed DNA polymerase, and ribonuclease activities (RNaseH) [6]. The tetramer form of the integrase is effective in the assimilation of proviral DNA with affected host cell genetic material. The precursor Env protein functions with mRNA and undergoes enzymatic processing by host cell proteases to liberate surface gp120 (SU) and transmembrane gp41 (TM) components [7]. The SU protein exhibits gp160 induced viral entry, and TM performs the gp41 mediated virus fusion into the host cell. The regulatory proteins Tat and Rev, generated during cleavage, are important for the viral replication process. Simultaneously, the accessory proteins, such as Vif, Vpr, Vpu, and Nef, are investigated as preferential fractions indispensable for virus propagation in the viral life cycle [8, 9]. The Pal and Env region proteins are shown in Fig. (**3**).

CHAPTER 6

A Review on Synthesis, Chemistry, and Medicinal Properties of Benzothiazines and their Related Scaffolds

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Abstract:

Background: Sulfur and nitrogen heterocyclic systems, especially benzothiazine derivatives, play a vital role in the search for newer drugs due to a significant scientific interest owing to their broad range of synthetic values, various routes, and pharmacological properties. It is known that benzothiazines are divided into five units: 1,2-, 2,1-, 1,3-, 3,1-, and 1,4-benzothiazines. Incorporating two moieties (benzo and thiazine) increases the biological activity of both, and thus their values synthesize new heteropolycyclic systems. Considering their diverse roles in the biological area and synthesis chemistry, huge effects have been found in developing novel and efficient methodologies to synthesize various benzothiazine moieties with different substitutions.

Methods: The present chapter comprises an inclusive vision of new and straightforward synthetic strategies to afford benzothiazine and related systems. This chapter covers various reactions for synthesizing benzothiazines, such as alkylation, acylation, aroylation, halogenation, elimination, rearrangement, ring enlargement, reduction, and oxidation. Besides, it also includes other reactions, like cyclization, addition, condensation, cyclocondensation, metal/acid-catalyzed, hydrolysis, aminolysis, hydrazinolysis, complexation, and enantio/regioselective. Moreover, many benzothiazines have been evaluated for their therapeutic activity.

Result: The synthesis and chemical reactions of benzothiazines derivatives have been reported. The preparation approaches of some compounds have been found to involve many steps, and others one-pot, resulting in good to excellent yields. Also, many synthesized compounds have shown medicinal properties, such as aldose reductase,

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anti-inflammatory, analgesic, antimicrobial, antibacterial, antifungal, anticancer, antiviral, antioxidant, herbicidal, and anticarcinogenic, anti-tubercular, anti-anthelmintic, and antitumor probes.

Conclusion: The chapter covers various methods to synthesize benzothiazines and their derivatives, thereby displaying their biological activities.

Keywords: Aldose Reductase, Anti-Inflammatory, Analgesic, Antibacterial, Antiviral, Anticarcinogenic, Alkylation, Benzothiazines, Cu-Catalyzed, Coupling, Herbicidal, Medicinal Properties, Meloxicam, Regioselectivity, Synthesis.

INTRODUCTION

Recently, the heterocyclic compounds, especially 1,2-benzothiazine nuclei, have received attention in pharmacological, medicinal, and agricultural areas [1 - 3]. Consequently, 1,2-benzothiazine derivatives have primarily been studied in different fields of chemistry, including pharmaceutical and other chemical industries. In addition, most of the 1,2-benzothiazine cores have several active sites, providing high responsiveness and making them excellent heterocyclic compounds.

1,2-Benzothiazines exhibit a wide range of medicinal applications, such as anti-inflammatory, analgesic, antibacterial, antiviral, herbicidal, fungicidal, and anticarcinogenic [4 - 10]. 1,2-Benzothiazine derivatives have attracted more significant scientific interest due to their synthesis values and medicinal properties [11]. These derivatives have a broad spectrum of pharmacological activities, such as anti-inflammatory, anti-HIV, and as anti-aldose reductase inhibitors [4, 12 - 17]. Moreover, various 3-carboxamide bearing 1,2-benzothiazine-1,1-dioxide compounds are associated with a family of oxicam, such as piroxicam, sudoxicam, isoxicam, and droxicam, which are considered non-steroidal anti-inflammatory drugs [18 - 20].

Besides, much focus has been directed towards the synthesis and construction of 1*H* -benzo [2, 1]thiazine derivatives and their medicinal properties, such as antibacterial [21], norepinephrine reuptake inhibitors [22], antioxidant [23], antiinflammatory, and analgesic activities [24, 25].

On the other hand, 1,3-benzothiazines are known to display a variety of biological activities, such as antibacterial [26, 27], analgesic [28], antimalarial [29], anti-inflammatory [30], antimicrobial [31], antimycobacterial [32], and antitumor [33]. Moreover, 3,1-benzothiazine structures have been introduced in several natural and synthetic active biological compounds. 3,1-Benzothiazines have been widely

applied in pharmaceutical and biochemical fields [34 - 38]. Also, some of their derivatives have interesting biological properties [39 - 42] and have attracted increasing attention.

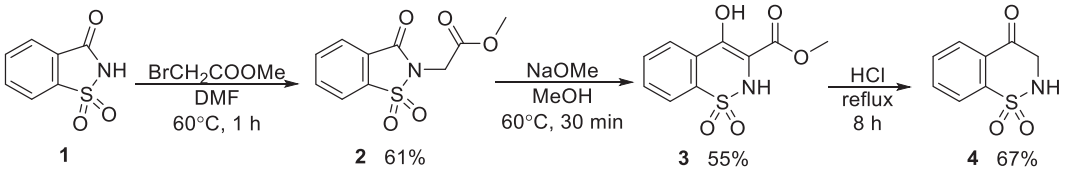
1,4-Benzothiazines are considered the backbone of S,N-heterocyclic compounds due to their exhibition of a vast range of pharmacological and biological properties, such as anti-inflammatory [43], antipyretic [44], antimicrobial [45], antiviral [46], antimalarial [47], anticancer [48, 49], antioxidant [50], herbicidal, and pesticidal [51].

Due to the above facts, this chapter focuses on the essential synthesis methods (from 2001 to 2021), the chemical reactions of all families of benzothiazines and their derivatives, and the critical medicinal properties.

SYNTHESIS

1,2-Benzothiazine Derivatives

2-(2-Substituted benzyl-1,1-dioxido-2,3-dihydro-4*H*-benzo[*e*] [1,2]thiazin-4- ylidene)acetic acids (**8a-f**) and 2-(2-substituted benzyl-1,1-dioxido-3, 4-dihydro-2*H*-benzo[*e*] [1, 2]thiazin-4-yl)acetic acids (**9a-d**) were obtained from the steps reported in Scheme. (**1** - **3**), starting from the alkylation of benzo[*d*]isothiazol- 3 (2*H*)-one 1,1-dioxide (**1**) with methyl 2-bromoacetate in DMF to produce compound **2**. The Gabriel-Colman rearrangement of compound **2** afforded the methyl 4-hydroxy-2*H*-benzo[*e*] [1, 2]thiazine-3-carboxylate 1,1-dioxide (**3**) by the expansion of the five-membered ring of **2** to the six-membered ring. Compound **3** underwent refluxing with conc. HCl for 8 h, yielding the 2,3-dihydro-4*H*-benzo[*e*] [1, 2]thiazin-4-one 1,1-dioxide (**4**) (Scheme. **1**) [16].



Scheme. (1). Synthesis of compounds **2-4**.

N-Substituted ketones **5a-e** were isolated from the alkylation of compound **4** by using substituted benzylic bromides in three steps. Reaction of **5** with methyl 2-(triphenyl-λ^5-phosphaneylidene) acetate in toluene at 100°C afforded the methyl 2-(2-(2-substitutedbenzyl)-1,1-dioxido-2,3-dihydro-4*H*-benzo[*e*] [1, 2] thiazin- 4-

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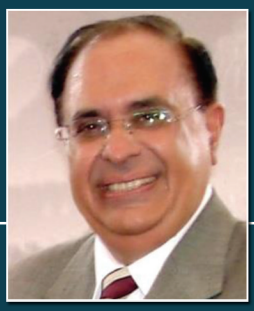

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Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.