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Abdul Rauf · Nida Nayyar Farshori

Microwave-Induced Synthesis of Aromatic Heterocycles

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Microwave-Induced Synthesis of Aromatic Heterocycles

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Preface

Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocycles. The importance of heterocycles provides a new basis for the development of new methods for their synthesis. Due to the strengthening environment regulations and safety concerns, there is a need of new innovative, environmentally friendly synthetic routes for synthesizing important heterocyclic compounds. Such synthesis can be designed using microwave technology. We therefore planned to publish a mini book that will include the microwave assisted synthesis of heterocyclic compounds. Although there are a large number of papers on the selected subject, however, we can only incorporate the recent references. We nevertheless extend our apologies to all the scientists whose research findings could not be cited or discussed in our mini book. The present book shall be of interest to all organic chemists as well as pharmaceutical and environmental chemists.

Abdul Rauf
Nida Nayyar Farshori

Contents

Chapter 1
Introduction to Microwave Chemistry

Abstract For more than a century heterocycles have constituted one of the largest areas of research in organic chemistry. The heterocyclic moieties are of exceptional interest in the pharmaceutical industry as they make up a core part of several drugs. The importance of heterocycles provides a significant basis for the development of new methods for their synthesis. Further, due to the strengthening environmental regulations and safety concerns, the industries are in need of new innovative, environmental friendly alternate routes for synthesizing the therapeutic and pharmacological important heterocyclics are desired. This environmentally benign synthesis can be easily designed using microwave methodology. The microwaves induce rapid heating and avoid the harsh classical conditions, resulting in the formation of cleaner products. The first chapter thus deals with the microwave theory, latest developments in instrumentation technology, the various microwave technologies used for synthesis.

Keywords Introduction · Theory · Equipments · Safety precautions · Heterocyclic synthesis

High-speed microwave synthesis has attracted a considerable amount of attention in recent years [1]. There is an increased interest in technologies and concepts that facilitate more rapid synthesis and screening of chemical substances to identify compounds with appropriate qualities. One such high-speed technology is a microwave-assisted organic synthesis (MAOS). Since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye [2] in 1986, more than 2,000 articles have been published in the area of MAOS [3]. The MAOS technology facilitates the discovery of novel pathways, because the extreme reaction conditions attainable by microwave heating sometimes lead to unusual reactivity that cannot always be duplicated by conventional heating. The initial slow uptake of the technology in the late 1980s and early 1990s has been attributed to its lack of controllability and reproducibility, coupled with

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a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns. Although most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens, the current trend clearly is to use dedicated instruments for chemical synthesis which have become available only in the last few years. Since the late 1990s the number of publications related to MAOS has therefore increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and sometimes improve selectivity [4, 5]. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid reaction optimization, for the efficient synthesis of new chemical entities, or for discovering and probing new chemical reactivity. A large number of review articles [6–13] and several books [14–16] provide extensive coverage of the subject. Not surprisingly, interest in microwave-assisted organic synthesis (MAOS) from academic, governmental, and industrial laboratories has steadily increased in recent years.

1.1 Conventional Heating Methods Versus Microwave Heating

In all conventional means for heating reaction mixtures, heating proceeds from a surface, usually the inside surface of the reaction vessel. Whether one uses a heating mantle, oil bath, steam bath, or even an immersion heater, the mixture must be in physical contact with a surface that is at a higher temperature than the rest of the mixture. In conventional heating, energy is transferred from a surface to the bulk mixture, and eventually to the reacting species. The energy can either make the reaction thermodynamically allowed or it can increase the reaction kinetics. In conventional heating, spontaneous mixing of the reaction mixture may occur through convection, or mechanical means can be employed to homogeneously distribute the reactants and temperature throughout the reaction vessel. Equilibrium temperature conditions can be established and maintained. Although it is an obvious point, it should be noted here that in all conventional heating of open reaction vessels, the highest temperature that can be achieved is limited by the boiling point of the particular mixture. Thus, the reactants will continue to reside at a temperature maintained by the solvent, regardless of the reaction's need for additional energy for a complete transformation. However in order to reach a higher temperature in the open vessel, a higher-boiling solvent must be used.

Microwave heating occurs somewhat differently from conventional heating. First, the reaction vessel must be substantially transparent to the passage of microwaves. The selection of vessel materials is limited to fluoropolymers and

only a few other engineering plastics such as polypropylene, or glass fiber filled PEEK (poly ether-ether-ketone). Heating of the reaction mixture does not proceed from the surface of the vessel; the vessel wall is almost always at a lower temperature than the reaction mixture. In fact, the vessel wall can be an effective route for heat loss from the reaction mixture. Second, for microwave heating to occur, there must be some component of the reaction mixture that absorbs the penetrating microwaves. Microwaves will penetrate the reaction mixture, and if they are absorbed, the energy will be converted into heat. Just as with conventional heating, mixing of the reaction mixture may occur through convection, or mechanical means can be employed to homogeneously distribute the reactants and temperature throughout the reaction vessel.

In contrast to heating by conventional means, microwave irradiation raises the temperature in the whole reaction volume simultaneously, without intervention through the vessel wall. This means that the synthesis proceeds uniformly throughout the reaction vessel, reaching completion simultaneously. This effect so influences the general scalability of reactions as an identical temperature profile can be achieved regardless of the volume of the vessel. Thus, in conventional heating methods for organic synthesis the heat is basically transferred by conductance and the extent of transfer of energy to the system depends on the thermal conductivity whereas, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules present in the reaction mixture.

Microwave-assisted synthesis is, in many ways, superior to traditional heating. The ability to elevate the temperature of a reaction well above the boiling point of the solvent increases the speed of reactions by a factor of 10–1,000. Reactions are thus completed in minutes or even seconds. Yields are generally higher and the technique may provide a means of synthesizing compounds that is not available conventionally. Further since the reaction times are very short, a reaction procedure can be fully optimized in an hour, and the scope of the reaction can then be tested with a diverse set of substrates in the following hour. As a result, a fully optimized procedure and a range of products can be produced in the time it would take to run a single conventional reaction

Another notable feature of microwave energy transfer over conductive energy transfer is that the applied energy is available with an instant on/off control. As detailed above, microwave energy enables the reaction to proceed in a more controlled manner in a decreased time period. Controlling the kinetics of the reaction becomes easy when the control of the applied energy becomes more direct and precise.

1.2 Theory of Microwave Synthesis

There are two specific mechanisms of interaction between materials and microwaves: (i) dipole interactions and (ii) ionic conduction. Both mechanisms require effective coupling between components of the target material and the rapidly

oscillating electrical field of the microwaves. Dipole interactions occur with polar molecules. The polar ends of a molecule tend to align themselves and oscillate in step with the oscillating electrical field of the microwaves. Collisions and friction between the moving molecules result in heating. Broadly, the more polar a molecule, the more effectively it will couple with (and be influenced by) the microwave field. Ionic conduction is only minimally different from dipole interactions. Obviously, ions in solution do not have a dipole moment. They are charged species that are distributed and can couple with the oscillating electrical field of the microwaves. The effectiveness or rate of microwave heating of an ionic solution is a function of the concentration of ions in solution.

When a reaction mixture is subjected to microwave irradiation, the transfer of microwave energy takes place as a result of direct interaction with the electric component of the microwave field. This transfer of microwave energy is fast and occurs at a rate of $2 \times 10^{-9}\ s^{-1}$ at 2,450 MHz. Further it must be noted that unlike in the conductive heating methods, reaction involving microwave heating do not reach thermal equilibrium. Generally the reactants in organic reactions being typically polar and/or ionic in nature are better absorbers of microwave energy than their surrounding environment. As, the reactants move to the transition state, the ionic conductivities of reactants increase and the molecules becomes more receptive to microwave energy. As, a result the reactant molecules are receiving energy at a higher rate than it can dissipate, creating a non-equilibrium state.

This non-equilibrium state which arises due to microwave energy input results in the high instantaneous temperature (T_i) of the molecules. The T_i is not directly measurable and it must be greater than the temperature of bulk system (T_B), so as to satisfy the Arrhenius equation ($k = Ae^{-Ea/RT}$). Therefore, T_i and not T_B ultimately determine the kinetics of the reaction and this accounts for the faster rate observed in microwave reaction.

In microwave heating, the synthesis can be designed in such a way that the reactants absorb energy exclusively, leading to two advantages of microwave energy transfer over conductive heating. First, the energy transfer is direct to the absorbing reactants, allowing the full field energy to activate the reactants directly at molecular level. Second, the formation of a non-equilibrium state, forces the molecule to dissipate thermal energy into surrounding environment. This allows the reaction to take place at a lower temperature, with obvious advantages in terms of safety and the thermal stability of the molecule.

1.3 Equipments Used in Microwave Synthesis

- Domestic microwave oven. The cheapest and most popular equipment used in organic synthesis is the domestic microwave oven (with a limited power of 800–1,000 W). The distribution of electric field is heterogenous and the sample is always subjected to maximum power levels for varying time periods. In the

organic synthesis involving the use of domestic microwave ovens, the requirement of pre determination of hot spots has to be fulfilled [17]. Further the major drawback in the use of domestic microwave oven is that the reaction parameters such as pressure and temperature cannot be maintained or controlled.

- Modified microwave ovens. The accuracy and safety factor in microwave assisted organic synthesis can be increased by causing a slight variation in domestic microwave oven. The modified microwave oven differs from domestic microwave oven in having a hole on top of cavity. This allows the introduction of a tube (acting as an air cooler) surmounted by a water cooler to maintain reaction's solvent reflux or under inert atmosphere, or allowing the chemist to follow multistep procedures of chemical synthesis.
- Commercially available microwave reactor. The specialized microwave reactors commercially available are equipped with various features including build-in-magnetic stirrer, direct temperature control of reaction mixture, with the aid of fiber optic probes or infrared sensors and software that enable on-line temperature and pressure control by regulation of microwave power output. Currently two different microwave reactors are emerging viz. multimode and monomode reactors. In multimode instruments, the microwaves entering the large cavity are reflected by the walls of cavity and therefore interact with the sample in a chaotic manner. On the other hand, in monomode instruments, the microwave irradiation is directed through a circular or rectangular wave guide on the reaction vessel that is mounted at a fixed distance from radiation source.
- Biotage microwave synthesizer. Recently Biotage have introduced a new microwave synthesizer, named Initiator^{TM}. Initiator is a flexible microwave synthesizer for fast, safe and scalable organic synthesis. The new, compact design of the Initiator^{TM} is 45% smaller than its predecessors. The sample can be loaded and run in just a few simple steps using the new embedded touch screen control and graphical-user-interface. With the EXP upgrade, the system can run 0.2−20 ml vials. For automated operation, an 8 or 60-position robotic assembly can be added at any time. The Initiator^{TM} is designed to operate at elevated temperatures and pressures with best-in-class safety features.

In view to increase in number of microwave synthesized organic reactions and advancement in technology most companies developing microwave instruments for commercial applications offer a variety of diverse reactor platform with different degrees of sophistication with respect to automation, database capabilities, safety features, temperatures and pressures monitoring and vessel design.

1.4 Safety Precautions in Microwave Synthesis

Although all measures have been taken by microwave apparatus manufacturers to make microwave a safe source of heating in chemical reactions, uncontrolled reaction conditions may lead to undesirable results such as excessive heating of volatile reactants may result in explosive conditions. The improper use of

microwaves for reactions involving radioisotopes may lead to uncontrolled radioactive decay. Further on, while conducting polar acid-based reactions the coupling of acid with microwaves raises the temperature to a very high value which may cause damage to the polymer reaction vessel.

To decrease the probability of explosion during a microwave assisted synthesis under sealed vessel condition, involving volatile products, the chemists have used open vessel solvent-free conditions [4, 18].

Moreover in spite of maintaining the best reaction conditions while performing MAOS there may exist certain loopholes. In such a condition following cautions need to be taken:

- The user must pre-inquire about the basic parameters of microwave apparatus being used, which may include the model no., year of manufacturing, serial no., wattage etc.
- During the time period when the reactants are being irradiated with microwave radiation, the reaction should be visually monitored.
- In case of any discrepancy in microwave apparatus, such as, loose doors, broken switches, penetration of metal enclosures etc., the apparatus should be immediately repaired or exchanged.

1.5 Coupling of Microwave Radiation with Solvent Free Heterocyclic Synthesis

Avoiding the use of organic solvents during MAOS of heterocycles lead to a clean, efficient and economical technology (Green Chemistry). Apart from this the safety is increased, workup is considerably simplified, cost is reduced, the use of toxic solvents can be avoided and the reactivities and sometimes the selectivities can also be enhanced without dilution. Due to these positive aspects of solvent free synthesis, there is a marked increase in the use of environmentally benign reagents and procedures.

The three types of solvent free procedures that can be coupled with microwave activation can be listed as:

- Reaction between neat reactants. The reaction between neat reactants may take place provided that there is present at least on polar molecule [19] as a liquid–liquid or liquid–solid systems. In case of liquid–solid systems the solubilization of solid in liquid phase or adsorption of liquid on solid surface as interfacial reaction takes place. In this type of reaction the effect of microwave irradiation is more pronounced due to the fact that in absence of solvent the microwaves are directly absorbed by the reagent.
- Reaction on solid mineral support. Reaction between supported reagents on solid mineral supports in “dry media” by impregnation of compounds on alumina, silica or clay takes place. The reactants are impregnated on solid

support as neat liquids or by using their solution in adequate organic solvent, the solvent is eliminated and dry media reaction is performed between impregnated reactants, followed by heating. When the reaction is completed the organic product is eluted with appropriate solvent.

- Phase transfer catalysis reaction. In absence of organic solvents, the liquid reactant may act both as a reagent and an organic phase, thus resulting in phase transfer catalysis condition. This method is specifically used for anionic reactions occurring between neat reactants in quasiequivalent amounts in presence of a catalytic amount of tetra-alkylammonium salts or cation complexing agents.

1.6 Application of Microwave Activation in Heterocyclic Chemistry

The importance of heterocycles in many fields of science (including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, medical and material science) can hardly be overemphasized and justifies a long lasting effort to work out new synthetic protocols for their production. Infact, the preparation of heterocycles by microwave irradiation constitutes one of the main growing fields of MAOS and it has been reviewed at several occasions [20]. It must be noted here there are a number of applications of microwave technology being used for the rapid synthesis of biologically active heterocyclic compounds. The recent development in the field of microwave technology is the use of this technology for the drug discovery program especially in combinatorial chemistry.

In, this mini book we have focused our attention to the application of microwave irradiation in synthesis of various important heterocyclic organic compounds viz. pyrazoles, imidazoles, oxazoles, thiazoles, oxadiazoles, oxazolines, triazoles, triazines, benzimidazoles, benzoxazoles and benzthiazoles. The selected heterocyclic moieties are synthetically important due to their interesting pharmacological properties (anti-HIV, anti-parasitic, anti-histaminic, anti-cancer, anti-malarial etc.).

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Chapter 2
Oxazoles

Abstract Oxazoles are a class of heterocyclic compounds that are believed to occur in nature from post-translational modification of serine and threonine residues in peptides. They are the key building blocks of natural products, pharmaceuticals, and synthetic intermediates. Oxazoles have not only attracted great interest due to their appearance as subunit of various biologically active natural products but also because of their utilities as valuable precursors in many useful synthetic transformations. Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities, such as hypoglycemic, anti-inflammatory, and antibacterial activities Currently also there is a large interest in developing new methodology for the preparation of oxazoles. The various methods for the synthesis of oxazole derivatives and their biological applications have been discussed in this chapter.

Keywords Oxazoles · Tandem alkylation/cyclisation · Cornforth rearrangement · Anti-proliferative agent · Antibacterial activity

Oxazoles are a class of heterocyclic compounds that are believed to occur in nature from post-translational modification of serine and threonine residues in peptides [1, 2]. They are the key building blocks of natural products, pharmaceuticals, and synthetic intermediates [3–5]. Oxazoles have not only attracted great interest due to their appearance as subunit of various biologically active natural products but also because of their utilities as valuable precursors in many useful synthetic transformations [6]. Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities, such as hypoglycemic [7], anti-inflammatory [8], and antibacterial [9] activities. It is reported that new D2-isoxazoline derivatives can be as β adrenergic receptor antagonists [7]. The oxazole derivatives have raised considerable attention to medicinal research, and a large number of investigations on their synthesis and biological activities have been reported during the last 10 years [10–12]. Currently

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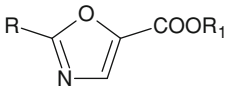
also there is a large interest in developing new methodology for the preparation of oxazoles.

Credico et al. [13] gave the selective synthesis of 2-substituted-4-carboxy oxazoles **(i)**. They optimized the mild and selective procedure so that the 2-substituted-4-carboxy derivatives can be obtained in multi-gram scale. Ball et al. [14] synthesized the various triazole derivatives **(ii),** bearing the oxazole ring system via a tandem alkylation/cyclisation reaction, exploiting a facilitating 'dummy' bromine atom.



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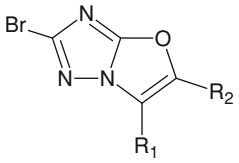
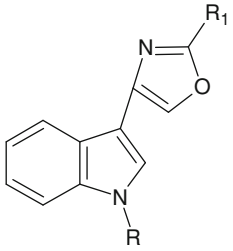


ii

R = Py, PhCOOMe, PhCOOMe **R_1** = H, CH_2CH_3, $CONMe_2$, CH_3, $COCH_3$

R_1 = Bn, Et **R_2** = CH_3, COOEt, CF_3, Ph

A series of 4-(3′-indolyl) oxazoles congeners **(iii)** have been synthesized under microwave condition and have been studied for their cytoxicity against six cancer cell lines by Kumar et al. [15]. The oxazoles were obtained in good yields.



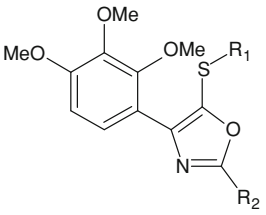
iii

R = H, CH_3, $4ClC_6H_4$

R_1 = C_6H_5, CH_3, 4-HOC_6H_4, 4-FC_6H_4-4-pyridyl, H, $CH{=}CH_2$, piperidin-4-yl

Liu et al. [16] synthesized twenty novel 2,4,5-trisubstituted oxazole derivatives **(iv)** containing heterocycle moiety and evaluated them for their antiproliferative activity. They showed that the microwave irradiation promoted the rapid O,N-acylation-cyclodehydration cascade reaction of oximes and acid chlorides.

The similar methodology was adopted by Wipf et al. [10] for the synthesis of various oxazoles.



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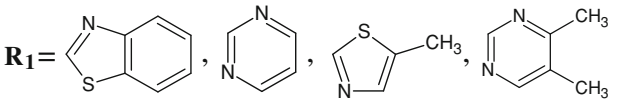
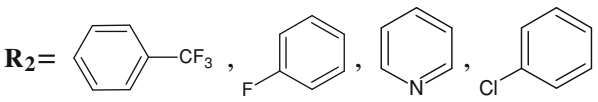
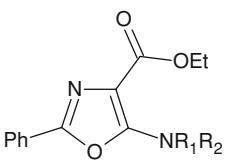
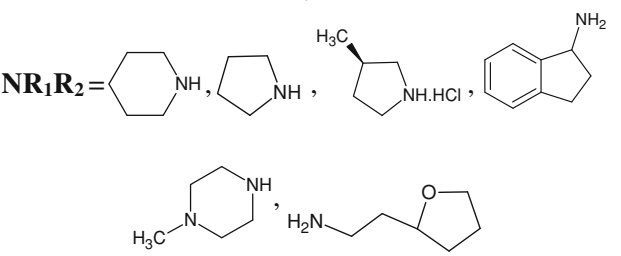




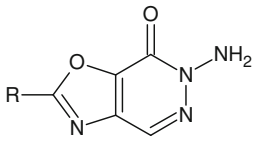
The 2-aryloxazoles have also been synthesized under microwave activation by the direct Stille and Suzuki cross-coupling reactions of 1,3-oxazoline (OXT) [17]. Nolt et al. [18] utilized the microwave-assisted Cornforth rearrangements for the preparation of substituted 5-amino-oxazole-4-carboxylate **(v).**



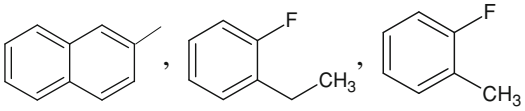
v



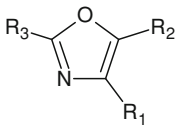
Frolov et al. [19] reported the formation of oxazole ring **(vi)** by the reaction of 5-amino-4-hydroxy-3(2H)-pyridazinone with various carboxylic derivatives using a microwave assisted procedure.



vi

R = 

The multi-substituted oxazoles **(vii)** have been synthesized by Lee et al. [20]. The carbonyl compounds were used as the starting materials and the synthesis was carried out under solvent free microwave conditions.

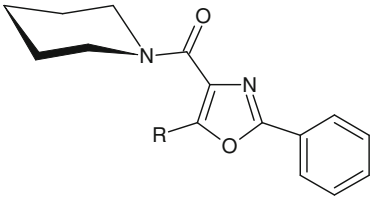


vii

R_1 = Ph, p-MeC_6H_4, p-ClC_6H_4, Me **R_2** = H, Me, COOMe, $CONEt_2$, COOEt

R_3 = Me, Ph

Clapham et al. [21] utilized the α-diazo-β-ketoester for the synthesis of an array of oxazoles **(viii)**



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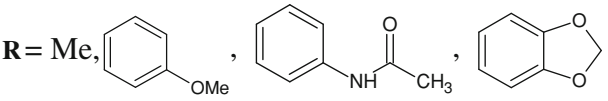

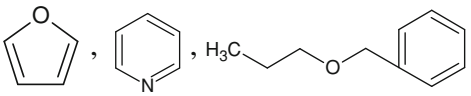

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Chapter 3
Thiazoles

Abstract The thiazole ring system is commonly found in many pharmaceutically important molecules. Numerous natural products containing this heterocycle have been isolated and exhibit significant biological activities such as cytotoxic, immunosuppressive, antifungal, and enzyme inhibitory activity. Moreover, among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process and this ring structure is found in several marketed drugs. It can also be used in a scaffold hopping strategy or as an amide isostere during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a core structure for the synthesis of chemical libraries. In the course of a lead generation effort, several flexible methods, amenable to the high throughput chemical synthesis of appropriately substituted thiazoles have been developed. Some of these methods have been cited in this chapter.

Keywords 1,2/1,3-Thiazoles · Carbohydrate derivative · Hantzsch protocol · MCH-1 receptor · Antiviral activity

The thiazole ring system is commonly found in many pharmaceutically important molecules. Numerous natural products containing this heterocycle have been isolated and exhibit significant biological activities such as cytotoxic, immunosuppressive, antifungal, and enzyme inhibitory activity [1, 2]. Moreover, among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process [3] and this ring structure is found in several marketed drugs. It can also be used in a scaffold hopping strategy [4] or as an amide isostere [5, 6] during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a core structure for the synthesis of chemical libraries [7]. In the course of a lead generation effort, several flexible methods, amenable to the high throughput

A. Rauf and N. N. Farshori, *Microwave-Induced Synthesis of Aromatic Heterocycles*, SpringerBriefs in Green Chemistry for Sustainability,
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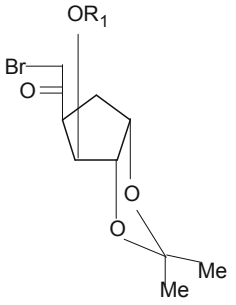
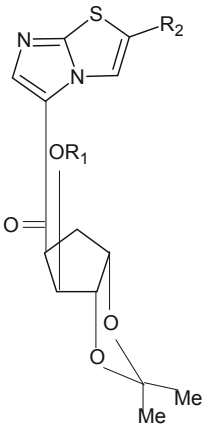
chemical synthesis of appropriately substituted 2,4,5-trisubstituted thiazoles have been developed.

Barradai et al. [8] described the synthesis of imidazo[2,1-b]thiazole carbohydrate derivatives **(ii)**. The substituted imidazo[2,1-b]thiazoles were obtained by a convergent synthetic pathway from either 6-bromo-6-deoxy-1,2-O-isopropylidene-3-O-methyl-α-D-xylo-hexofuranos-5-ulose/6-bromo-6-deoxy-1,2-O-isopropylidene-3-O-methyl-α-D-xylo-hexofuranos-5-ulose **(i)**. The synthesized derivatives proved to be potential antiviral agents.



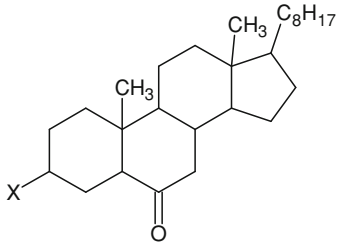
i



ii

$\mathbf{R_1}$ = CH_3,$COCH_3$ $\mathbf{R_2}$ = COC_6H_5, COC_6H_4Br-p, COC_6H_4Cl-p, COC_6H_4F-p

Khan et al. [9] reported the environment friendly microwave-assisted synthesis of substituted steroidal[6,7-d]thiazoles **(iv)**. The key step involved the reaction of α-haloketones **(iii)** and thiourea/substituted thiourea via hantzsch protocol.



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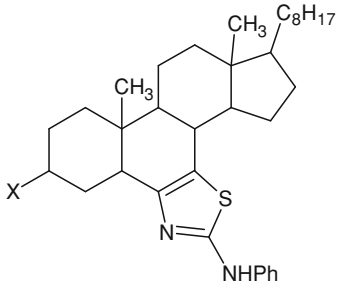
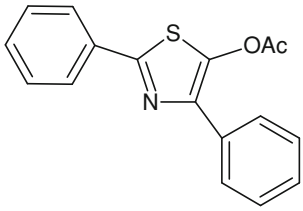


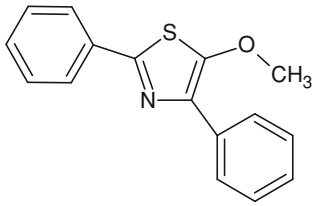
iv

X = H, OAc, OPr

A highly flexible synthesis of 2,4,5-trisubstituted thiazoles **(vi)** by in situ hydrolysis and alkylation of 2,4-disubstituted-5-acetoxythiazoles **(v)** has been described by Qiao et al. [10].

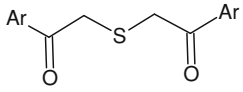


v

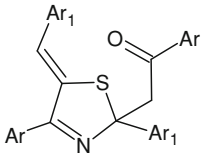


vi

Renuga et al. [11] stereoselectively synthesized the series of thiazoles **(viii)** by the reaction of bis(aroylmethyl)sulfides **(vii)** with aromatic aldehydes and ammonium acetate in the molar ratio of 1:2:1 under solvent free microwave conditions.



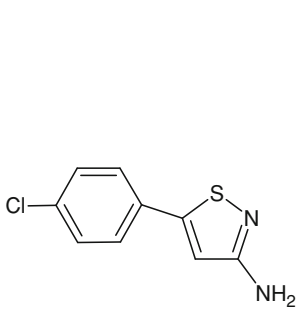
vii



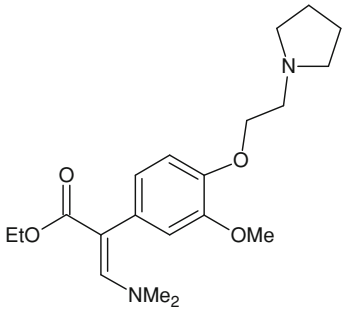
viii

Ar = C_6H_5, p-Cl-C_6H_4, p-MeC_6H_4 **Ar1** = C_6H_5, p-Cl-C_6H_4, p-MeC_6H_4

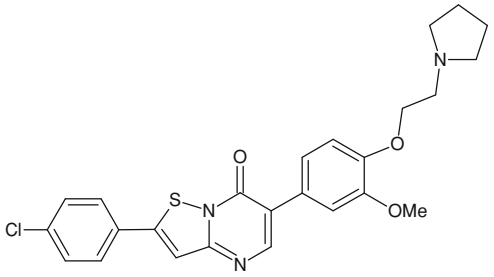
Various thiazolo-heterocyclic compounds **(xi)** as novel MCH 1R antagonist (MCH-1 receptor) have also been effectively synthesized by Guo et al. [12]. The reaction involved the microwave assisted condensation of α-heteroarylamines **(ix)** with 3-dimethylamino-2-aryl-propenoates **(x)**.



ix

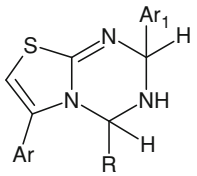


x



xi

Yadav and Kapoor [13] synthesized the acyclic C-nucleosides **(xii)** incorporating the thiazole-s-triazine structure as a nucleobase following a three-component, one-pot reaction under solvent free condition and microwave irradiation.



xii

Ar = Ph **Ar$_1$** = Ph, 4-MeOC$_6$H$_4$ **R** = D-arabinobutyl, D-ribobutyl, D-glucopentyl

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Chapter 4
Oxazolines

Abstract Oxazolines are known as important heterocyclic compounds and have been investigated widely for pharmaceutical uses. The efficiency of oxazoline analogues as chemotherapeutic agent especially as analgesic and anti-inflammatory agent is well documented. In addition to pharmaceutical uses it also possesses synthetic uses, for example it can catalyze the coppercatalyzed addition of indoles to benzylidene malonates up to 99%. Further, oxazolines have emerged as a very interesting class of heterocycles with an astonishingly wide range of applications in synthetic organic chemistry. Oxazolines have been of great interest due to their versatility as protecting groups, as chiral auxiliaries in asymmetric synthesis, and as ligands for asymmetric catalysis. In view to the known importance of oxazoles, a large number of synthetic protocols have been developed. A few of them have been cited in chapter.

Keywords Oxazolines · Direct Stille and Suzuki coupling · Diisopropylcarbodiimide cyclization · Chemotherapeutic agent · Anti-HIV activity

Oxazolines are known as important heterocyclic compounds and have been investigated widely for pharmaceutical uses [1]. The efficiency of oxazoline analogues as chemotherapeutic agent especially as analgesic [2] and anti-inflammatory [3] agent is well documented. Besides, additional functionalities for targeting can readily be introduced into 2-oxazolines via functional monomer units, these compounds fulfils fundamental requirements for an application as carrier molecules in radionuclide therapy [4]. Recent studies have shown that highly active sugar oxazolines act as donor substrates for transglycosylation and exhibit potent anti-HIV activity [5]. Oxazoline analogues have been shown to induce cell growth inhibition, apoptosis, and microtubule disruption without alkylating beta-tubulin [6]. And polyoxazoline-based polymers have shown biological and biomedical application contexts which include nanoscalar systems such as membranes and nanoparticles, drug and gene

A. Rauf and N. N. Farshori, *Microwave-Induced Synthesis of Aromatic Heterocycles*, SpringerBriefs in Green Chemistry for Sustainability,
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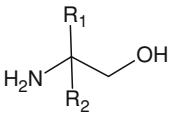
delivery applications, as well as stimuliresponsive systems [7]. In addition to pharmaceutical uses it also possesses synthetic uses, for example it can catalyze the coppercatalyzed addition of indoles to benzylidene malonates up to 99% [8].

Further, oxazolines have emerged as a very interesting class of heterocycles with an astonishingly wide range of applications in synthetic organic chemistry [9]. Oxazolines have been of great interest due to their versatility as protecting groups [10], as chiral auxiliaries in asymmetric synthesis [11], and as ligands for asymmetric catalysis [12].

Sharma et al. [13] synthesized the 2-oxazolines **(iii)** using the microwave assisted open vessel technique. The synthetic protocol involved the direct condensation of carboxylic acids with excess of 2-amino-2-methyl-1-propanol **(i)** at 170 °C.



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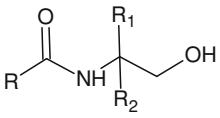
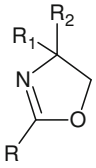


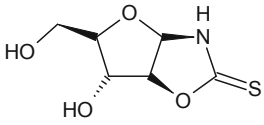
ii



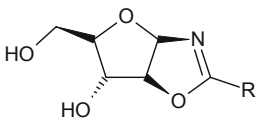
iii

R_1 = R_2 = H, CH_3, CH_2OH

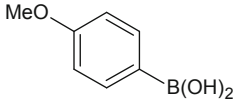
The 2-aryloxazolines **(v)** have been synthesized under microwave activation by the direct Stille and Suzuki cross coupling reactions of 1,3-oxazolidine-2-thiones (OZT) **(iv)** using **(vi)** as the coupling agent [14].



iv



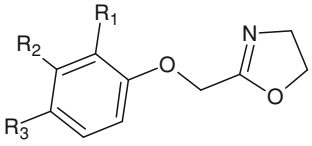
v



vi

R= MeOPh, 2-thiophen

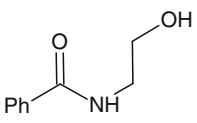
Khanum et al. [15] reported the synthesis of biologically active 2-aryloxy methyl oxazolines **(vii)** from substituted hydroxybenzenes in good yields.



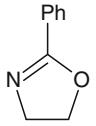
vii

R_1 = H, Br, Cl, CH_3, NO_2 **R_2** = H, CH_3, NO_2 **R_3** = H, Cl, OCH_3, NO_2

Crosignani et al. [16] synthesized the 2-oxazolines **(ix)** in high yields from the cyclization of N-(β-hydroxy)amides **(viii)** by diisopropylcarbodiimide (DIC) under microwave irradiation.

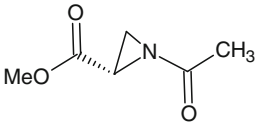


viii

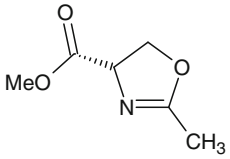


ix

The microwave-assisted ring exposure of N-acyl activated aziridines **(x)** to oxazolines **(xi)** is reported by Cardillo et al. [17].



x



xi

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Chapter 5
Oxadiazoles

Abstract Microwave assisted synthesis in organic chemistry is an important and a well established area of research due to a number of advantages over conventional heating methods. Further, nitrogen heterocycles of different ring sizes, with different substitution patterns and embedded in various molecular frameworks constitute extremely important structure classes in the search for bioactivity. Many compounds bearing five-membered heterocyclic rings in their structure have an extensive spectrum of pharmacological activities. Among them oxadiazoles and their derivatives have attracted considerable interest in material and medicinal chemistry as surrogates of carboxylic acids, esters and carboxamides. The various oxadiazole compounds have shown a wide array of biological activities in both agrochemical and pharmaceutical fields. The formation of this biologically important heterocyclic system under microwave conditions is described in this chapter.

Keywords 1,3,4-Oxadiazoles · Organomercurials · Sugar derivatives · Cytotoxic · Antifungal activity

Microwave assisted synthesis in organic chemistry is an important and a well established area of research due to a number of advantages over conventional heating methods [1]. Further, nitrogen heterocycles of different ring sizes, with different substitution patterns and embedded in various molecular frameworks constitute extremely important structure classes in the search for bioactivity. Many compounds bearing five-membered heterocyclic rings in their structure have an extensive spectrum of pharmacological activities. Among them oxadiazoles and their derivatives have attracted considerable interest in material and medicinal chemistry as surrogates of carboxylic acids, esters and carboxamides [2]. The various oxadiazole compounds have shown a wide array of biological activities in both agrochemical and pharmaceutical fields showing anti-convulsant [3], anti-microbial [4], insecticidal [5], fungicidal [6], anti-inflammatory [7],

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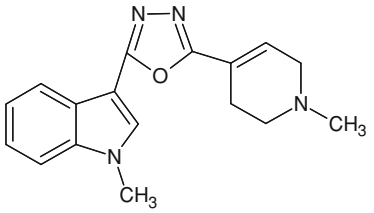
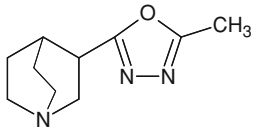
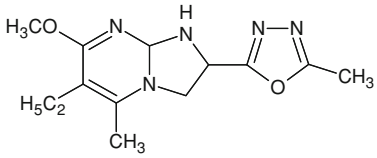
anti-leishmanial [8], hypotension [9] and anti-tumor [10] characteristics. Some of the members belonging to 1,3,4-oxadiazole class display 5-HT-receptor antagonists **(i)** [11], muscarinic receptor agonists **(ii)** [12], benzodiazepine receptor agonists **(iii)** [13] and tyrosinase inhibitors [14].



i

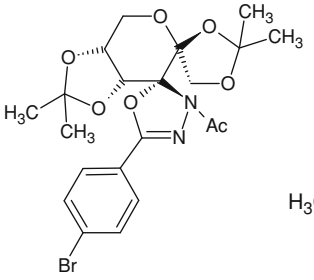


ii

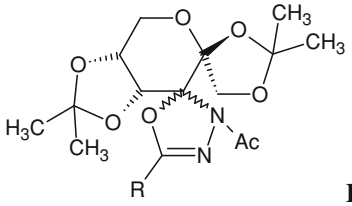


iii

A fructose based 3-acetyl-2,3-dihydro-1,3,4-oxadiazole (GLB) **(iv)** and its 5-linear 5-alkyl derivatives **(v)** have shown some cytotoxic activities [15].



iv



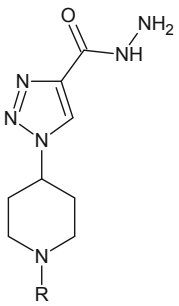
R = linear alkyl

v

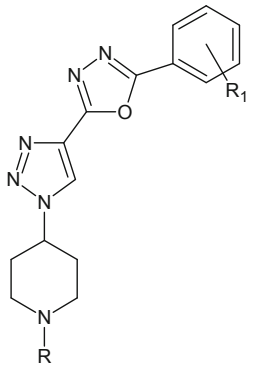
The most general method involves the cyclization of diacylhydrazides with a variety of reagents such as thionyl chloride, phosphorus oxychloride and sulphuric acid, usually under harsh reaction conditions. Further, most of these protocols are multi-step in nature and involve long reaction times. Only a few reliable and operationally facile examples have been reported for the one step synthesis of oxadiazoles, especially from readily available carboxylic acids and acid hydrazides [16, 17].

Thus, in an attempt to overcome these disadvantages of classical thermal reactions the microwave technique for the synthesis of 1,3,4-oxadiazoles has rapidly gained acceptance.

Sangshetti et al. [18] synthesized a novel series of 1,3,4-oxadiazoles **(vii)** by a one pot reaction of hydrazide **(vi)**, aromatic aldehyde in ethanol:water using sodium bisulfate as the catalyst. All the compounds showed good antifungal activities.



vi



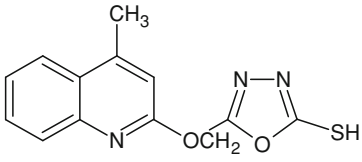
vii

R = CH_3, CH_2CH_3, SO_2CH_3, COC_6H_5

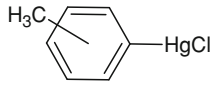
R_1 = OCH_3, NO_2, CH_3

Rostamizadeh et al. [19] found potassium fluoride to be an efficient catalyst and solid support for the one-pot solvent-free synthesis of 3,5-disubstituted-1,2,4-oxadiazoles.

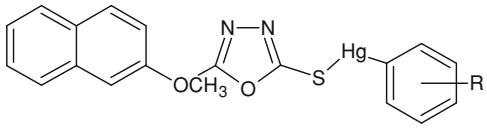
The organomercurials, 2-(aryl mercurithio)-5-[4′-methylquinolinyl-2-oxy methyl]-1,3,4-oxadiazoles **(x)** were synthesized by reacting 2-mercapto-5-[4′-methylquinolinyl-2-oxymethyl]-1,3,4-oxadiazole **(viii)** in DMF, anhydrous K_2CO_3 and aryl mercuric chloride **(ix)** under microwave irradiation [20].



viii



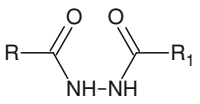
ix



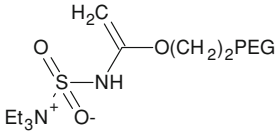
x

R= H, 4-CH_3, 4-Cl, 4-Br, 4-OCH_3

A novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines **(xi)** using polymer-supported burgess reagent **(xii)** under microwave conditions is described by Brain et al. [21].

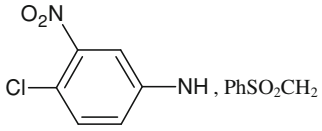


xi



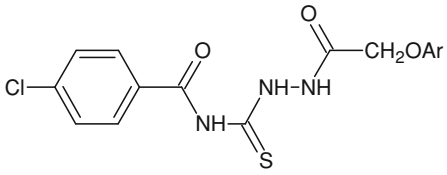
xii

R = Ph, 2-Methoxyphenyl, 2-Chlorophenyl, 2-Nitrophenyl, 2-Thiophenyl, 2-Furyl, 3-Pyridyl,

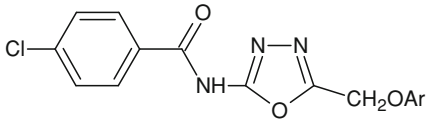


R_1 = Ph, Me, NHPh

Wang et al. [22] synthesized the 2-(4-chlorobenzoylamido)-5-aryloxymethyl-1,3,4-oxadiazoles **(xiv)** by the cyclization of 1-aryloxyacetyl-4-(4-chlorobenzoyl)-thiosemicarbazides **(xiii)** in the presence of mercuric acetate under the condition of microwave irradiation.



xiii

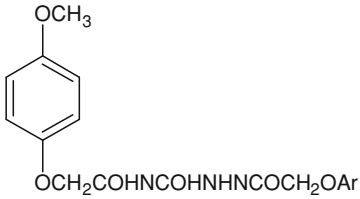


xiv

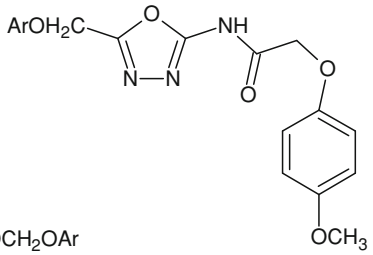
Ar = C_6H_5, 2-CH_3-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 1-Naphthyl, 4-Cl-C_6H_4

A series of 2,5-diaryl-1,3,4-oxadiazoles have been synthesized by reacting a mixture of corresponding aromatic acid, hydrazine dihydrochloride and phosphorus pentoxide in orthophosphoric acid under microwave conditions [23].

2-(4-Methoxylphenyloxyacetylamido)-5-aryloxymethyl-1,3,4-oxadiazoles **(xvi)** were synthesized by the cyclization of 1-aryloxyacetyl-4-(4-methoxylphenyloxy-acetyl)-thiosemicarbazides **(xv)** in presence of mercuric acetate under microwave irradiation [24].

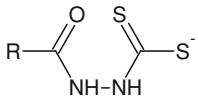


xv

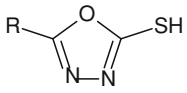


xvi

The microwave dielectric heating of potassium salt of 2-acyldithiocarbazinic acids **(xvii)** gave the 5-substituted-2-mercapto-1,3,4-oxadiazoles **(xviii)** in good yields [25].



xvii

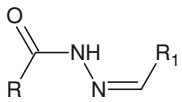


xviii

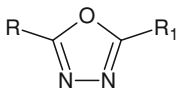
R = Ph, 4-Cl-C_6H_4, 4-$CH_3C_6H_4$, 4-Pyridyl, 4-OCH_3-C_6H_4, $C_6H_5CH_2$, 4-OH-C_6H_4

The 2,5-disubstituted-1,3,4-oxadiazoles were obtained by Mashraqui et al. [26] by condensing monoaryl hydrazides with acid chlorides in HMPA solvent under microwave heating.

2,5-Disubstituted-1,3,4-oxadiazoles **(xx)** were prepared by the oxidation of 1-aroyl-2-arylidine hydrazines **(xix)** with potassium permanganate on the surface of silica gel as well as in mixtures of acetone and water under microwave irradiation [27].



xix



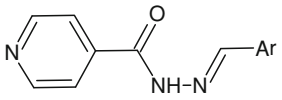
xx

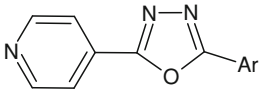
R = Ph, Me, 4-Cl-C_6H_4

R_1 = Ph, 4-$NO_2C_6H_4$, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-MeOOC-C_6H_4, 4-$(Me)_2N$-C_6H_4, Me, CH_3CH=CH, Ph.

Khan et al. [28] synthesized the 2,5-disubstituted-1,3,4-oxadiazoles from 3-pyridyl hydrazide and benzoic acid by microwave irradiation taking alumina as the solid support and phosphorus oxy chloride as a dehydrating agent .

The reaction of isonicotinic acid hydrazide and corresponding benzaldehyde under microwave conditions gave the heterocyclyl acylhydrazones **(xxi)**. The oxidation of **xxi** with iodobenzene diacetate (IBD) gave the heterocyclyl-1,3,4-oxadiazoles **(xxii)** in a solid state [29].

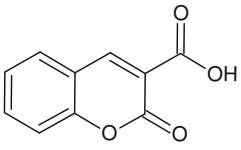


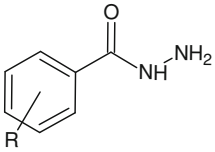


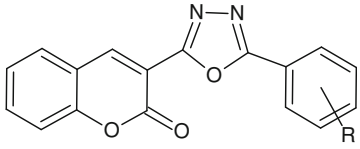
xxi **xxii**

Ar = C_6H_5, 4-$NO_2C_6H_4$, o-Cl-C_6H_4, m-$NO_2C_6H_4$, p-$NO_2C_6H_4$, p-$CH_3C_6H_4$, p-$OCH_3C_6H_4$, o-OH-C_6H_4, m-Cl-C_6H_4, -CH=CH-C_6H_5

Li et al. [30] gave the solvent free synthesis of 2-aryl-5-(coumarin-3′-yl)-1,3,4-oxadiazoles **(xxv)** in high yields by reacting the coumarin-3-carboxylic acid **(xxiii)** with (un)substituted benzoic acid hydrazides **(xxiv)** in presence of PEG supported dichlorophosphate under microwave irradiation.



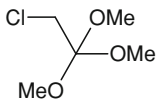


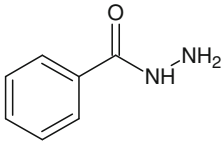


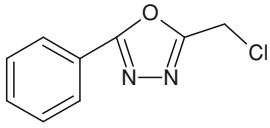
xxiii **xxiv** **xxv**

R = H, 2-Cl, 3-NO_2, 4-CH_3O, 4-I, 2-OH, 3-CH_3.

Natero et al. [31] gave the one-step synthesis of 5-phenyl-2-chloromethyl-1,3,4-oxadiazoles **(xxviii)** from commercially available acylhydrazides **(xxvii)** using 1-chloro-2,2,2-trimethoxyethane **(xxvi)** as a solvent under microwave conditions.



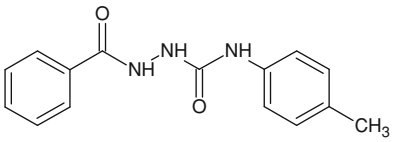




xxvi **xxvii** **xxviii**

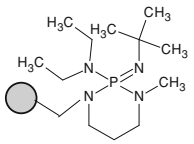
A library of 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized under microwave irradiation and screened for their tyrosinase inhibition activities [32].

A single pot synthetic protocol for the synthesis of 2-sulphonamide-1,3,4-oxadiazoles from 1,2-diacylhydrazine **(xxix)** under microwave irradiation using PS-BEMP **(xxxi)** and corresponding sulfonyl chloride **(xxx)** is reported by Baxendale et al. [33].



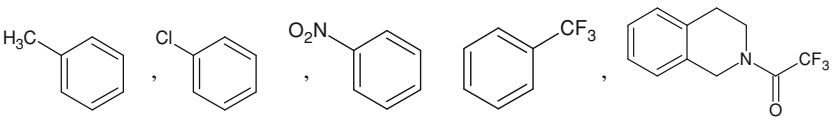
xxix

xxx

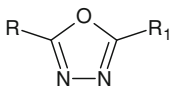


xxxi

R =

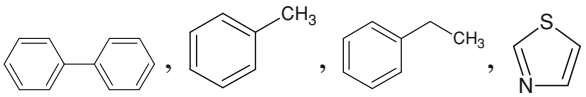


Wang et al. [34] gave the single step, rapid and efficient synthesis of 1,3,4-oxadiazoles **(xxxii)** from carboxylic acids and acid hydrazides by using commercially available PS-PPh_3 resin combined with microwave heating.

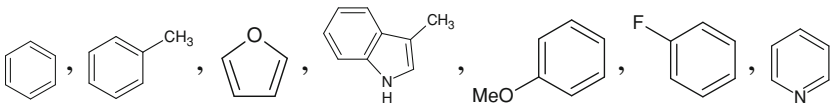


xxxii

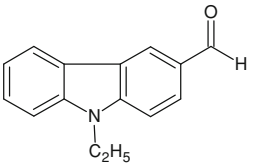
R =



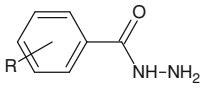
R_1 =



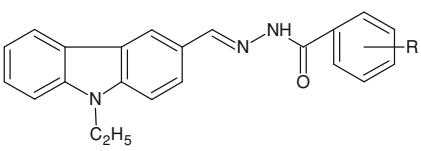
The reaction of 9-ethylcarbazol-3-carbaldehyde **(xxxiii)** with aroylhydrazines **(xxxiv)** under microwave condition gave the intermediate, 1-aroyl-2-(9′-ethylcarbazol-3′-yl-methylidene) hydrazines **(xxxv)**. The further treatment of **xxxv** with potassium permanganate in DMF under microwave irradiation afforded the 2-aryl-5-(9′-ethylcarbazol-3′-yl)-1,3,4-oxadiazoles **(xxxvi)** in excellent yields [35].



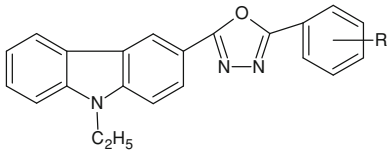
xxxiii



xxxiv



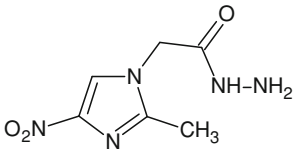
xxxv



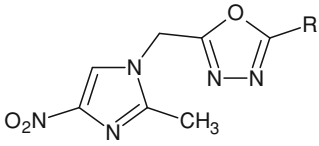
xxxvi

R = H, 4-Cl, 3-NO_2, 3-CH_3, 2-CH_3, 4-OH, 4-Br.

5-Substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles **(xxxviii)** have been prepared under microwave irradiation using 2-methyl-4-nitro-1-imidazo-acethydrazide **(xxxvii)**, aromatic acid and phosphorus oxychloride as the cyclizing agent [36].



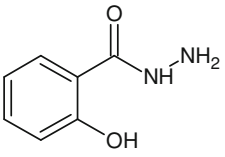
xxxvii



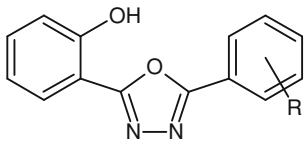
xxxviii

R = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-$CH_3C_6H_4$, C_6H_4N.

The synthesis of 5-aryl-2-(2-hydroxyphenyl)-1,3,4-oxadiazoles **(xL)** reacting salicylic hydrazide **(xxxix)** with carboxylic acids in the presence of thionyl chloride under neat conditions is described [37].



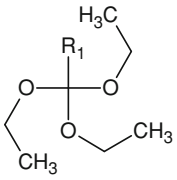
xxxix



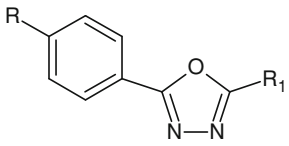
xL

R = H, 4-Me, 4-MeO, 3,4-$(MeO)_2$, 3,4,5-$(MeO)_3$, 3-Cl, 2-Br, 3-$MeOC_6H_4CH_2$.

Polshettiwar et al. [38] gave a novel, one-pot, solvent free, green protocol for the synthesis of 1,3,4-oxadiazoles **(xLii)** by the condensation of acid hydrazide and triethyl orthoalkanates **(xLi)** using solid supported Nafion®NR50 and phosphorus pentasulphide in alumina as a catalyst.



xLi



xLii

R = H,F, OMe, 2-Furyl, 2-Thienyl, 4-Pyridyl. **R_1**=H, Et, Ph.

An efficient one pot synthesis of unsymmetric 2,5-disubstituted-1,3,4-oxadiazoles has been developed by Pore et al. [39]. The target oxadiazoles were formed by the oxidation of acylhydrazones using trichloroisocyanuric acid (TCCA) at an ambient temperature.

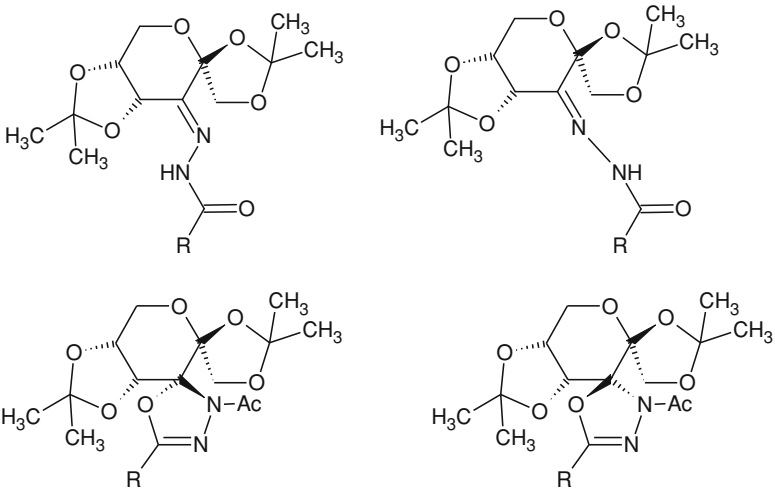
The microwave assisted synthesis of new lanthanum (III) and praseodymium (III) complexes with oxadiazole functionalized dithiocarbazinates, $[M(L)_3]$ is described [40].

M = La, Pr

L = N-(5-phenyl-1,3,4-oxadiazole-2-yl)dithiocarbazinate (PODC), N-(5-o-chlorophenyl-1,3,4-oxadiazole-2-yl)dithiocarbazinate (OCODC), N-(5-p-chlorophenyl-1,3,4-oxadiazole-2-yl)dithiocarbazinate (PCODC), N-(5-o-methylphenyl-1,3,4-oxadiazole-2-yl)dithiocarbazinate (MODC), N-(5-p-nitrophenyl-1,3,4-oxadiazole-2-yl) dithiocarbazinate (NODC).

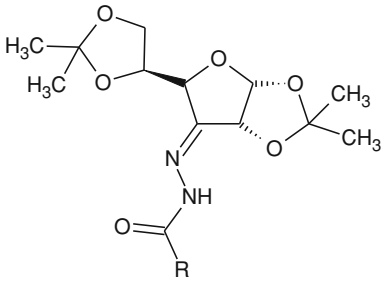
Han et al. [41] gave the microwave assisted synthesis of novel alkyl substituted fructose-based oxadiazoles and investigated them for their cytotoxic activity

towards cancer cells. The reaction of *E*-3-alkylhydrazono-1,2:4,5-di-O-isopropylidene-*β*-D-*erythro*-2-hexulopyranose **(xLiii)** and *Z*-3-alkylhydrazono-1,2:4,5-di-O-isopropylidene-*β*-D-*erythro*-2-hexulopyranose **(xLiv)** with acetic anhydride under microwave heating conditions gave (2*R*,3a′*R*,6′*S*,7a′*R*)-3-alkyl-2′,2′,2″,2″-tetermethyl-5-methyl-2,3-dihydro-1,3,4-oxadiazole-2-spiro-7′-(1′,3′-dioxalano[4,5-*c*]pyrano)-6′-spiro-4″-(1″,3″-diaoxolane) **(xLv)** and (2*S*,3a′*R*,6′*S*,7a′*R*)-3-alkyl-2′,2′,2″,2″-tetermethyl-5-methyl-2,3-dihydro-1,3,4-oxadiazole-2-spiro-7′-(1′,3′-dioxalano[4,5-*c*]pyrano)-6′-spiro-4″-(1″,3″-diaoxolane) **(xLvi)** in good yields.

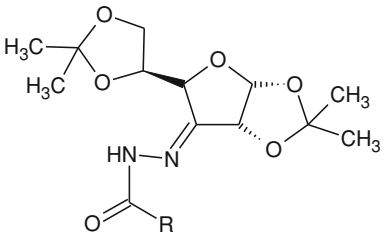


xLv **xLvi**

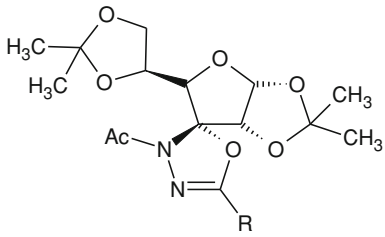
A novel approach to synthesize the glucose-based 3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazoles with the assistance of microwave irradiation was developed by Wang et al. [42]. The reaction of a mixture of *E*/*Z* hydrazones **(xLvii, xLviii)** with acetic anhydride under microwave irradiation above 160 °C, to produce the target 1,3,4-oxadiazoles **(xLix, L)**, which are a pair of isomers on the C-3 of furan ring.



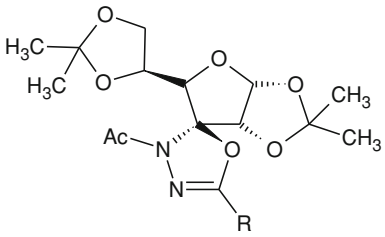
xLvii



xLviii



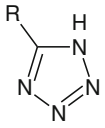
xLix



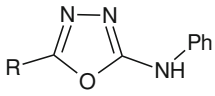
L

R = CH_3, n-C_3H_7, n-C_7H_{15}, C_6H_5, C_6H_4Br, C_6H_4OMe.

The reaction of 5-aryl (hetaryl)tetrazoles **(Li)** with phenyl isocyanate under the conditions of microwave activation formed the corresponding 2-anilino-5-aryl(hetaryl)-1,3,4-oxadiazoles **(Lii)** in high yields [43].



Li

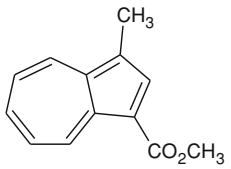


Lii

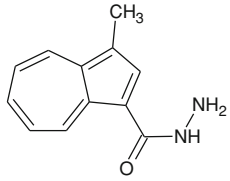
R = 4-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Furyl.

Xu et al. [44] reported the microwave assisted synthesis and antifungal activity of 2,5-disubstituted-1,3,4-oxadiazoles containing azulene moiety. The 5-aryl-2-(3-methylazulen-1-yl)-1,3,4-oxadiazoles **(Lv)** were obtained by the microwave

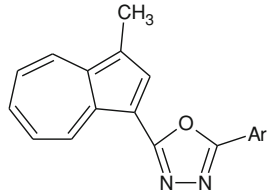
irradiation of corresponding hydrazide **(Liv)** with appropriate carboxylic acid ester **(Liii)** in presence of phosphorus oxychloride.



Liii



Liv



Lv

Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4, 2-BrC_6H_4, 2-OHC_6H_4, $C_6H_5CH{=}CH$, 4-$MeC_6H_5CH{=}CH$.

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Chapter 6
Pyrazoles

Abstract Pyrazoles are among the important scaffolds possessing various biological activities. Pyrazole and its derivatives are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities such as anti-bacterial, anti-depressant, and anti-hyperglycemic. The bioactivity of functionalized N-arylpyrazole was extensively studied and the C-5 substituted pyrazoles are also exploited in the design of pharmaceuticals and agrochemical agents. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as cannabinoid hCB1 and hCB2 receptor, anti-inflammatory, inhibitors of p38 kinase, CB_1 receptor antagonists, antimicrobial activity. Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known cyclooxygenase-2 inhibitor. As a consequence, much attention has been paid to the design and synthesis of pyrazole derivatives. A few of such synthetic protocols have been discussed in this chapter.

Keywords Pyrazoles · Silica-assisted solution phase synthesis · TSPO ligands · Analgesic · Anti-inflammatory

Pyrazoles are among the important scaffolds possessing various biological activities. Pyrazole and its derivatives are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities such as anti-bacterial, anti-depressant, and anti-hyperglycemic [1–3]. The bioactivity of functionalized N-arylpyrazole was extensively studied and the C-5 substituted pyrazoles are also exploited in the design of pharmaceuticals and agrochemical agents [4, 5]. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as cannabinoid hCB1 and hCB2 receptor, anti-inflammatory, inhibitors of p38 Kinase, CB_1 receptor antagonists, antimicrobial activity [6–8]. Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib **(i)**, a well-known cyclooxygenase-2 inhibitor [9, 10]. The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a

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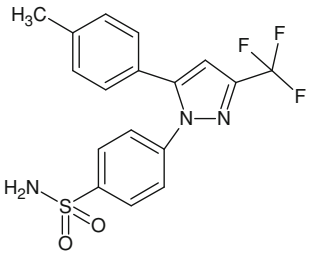
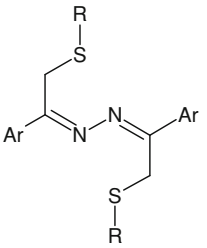
major strategy to obtain activity and safety advantages. As a consequence, much attention has been paid to the design and synthesis of pyrazole derivatives [11, 12].

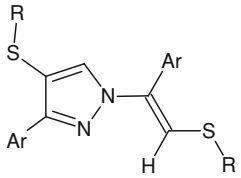


i

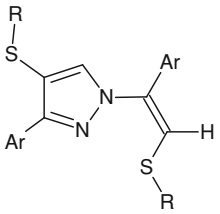
The two isomeric forms of pyroles **(iii**, **iv)** have been reported by the reaction of azines **(ii)** on treatment with excess phosphorus oxychloride in N,N-dimethyl formamide [13].



ii



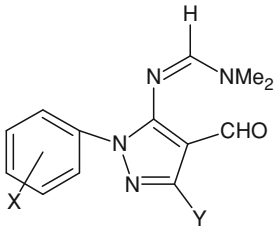
iii



iv

Ar = C_6H_5, p-ClC_6H_4, 2-napththyl **R =** p-ClC_6H_4, C_6H_{11}, C_6H_5

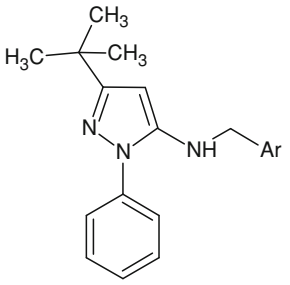
Cheng et al. [14] introduced an amidinyl group into the C-5 position of N-arylpyrazoles by the use of commercially available amide solvents and phosphorus oxychloride under microwave irradiation and a series of *N*,*N*-disubstituted-*N*′-[1-aryl-1*H*-pyrazol-5-yl]-methnimidamides **(v)** were obtained.



v

X = H, o-Cl, m-Me, m-NO_2 **Y =** Ph, p-MePh, t-butyl, p-Cl

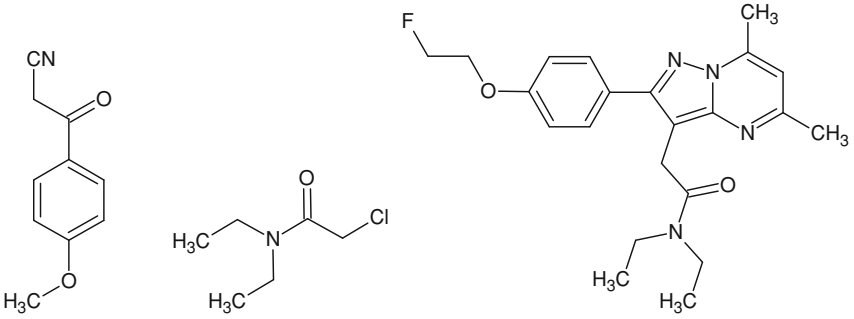
Quiroga et al. [15] proposed a simple microwave-assisted, one-step, three-component methodology for the synthesis of pyrazolo [3,4-b]pyridine-spiro cycloalkanediones from 5-aminopyrazole derivatives **(vi)**.



vi

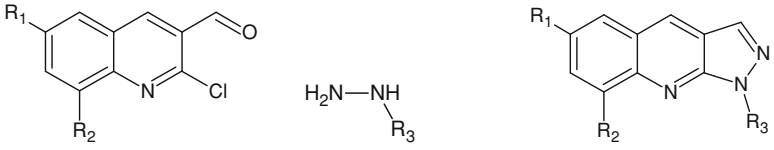
Ar = 4-ClC_6H_4, C_6H_5, 4-FC_6H_4 4-$CH_3C_6H_4$

The total synthesis of a high affinity TSPO (translocator protein) ligands, DPA-714 **(ix)**, starting from 3-(4-methoxyphenyl)-3-oxopropanenitrile **(vii)** and 2-chloro-N,N-diethylacetamide **(viii)** utilizing the microwave assisted organic synthesis (MAOS) has been described by Tang et al. [16].



vii **viii** **ix**

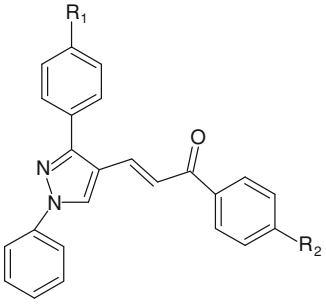
Mali et al. [17] for the first time carried out the condensation reaction of 2-chloro-3-formyl quinolines **(x)** and hydrazine hydrate/phenyl hydrazine **(xi)** under microwave irradiation for the synthesis of pyrazolo [3,4-b]quinolines **(xii)**.



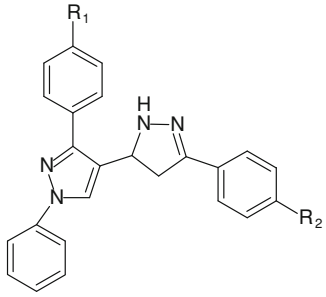
x **xi** **xii**

R_1 = H, OMe, Me **R_2** = H, Et **R_3** = H, Ph

The formation of the racemic pyrazoles **(xiv)** by the microwave assisted cyclocondensation reaction of a chalcones **(xiii)** has been reported by Insuasty et al. [18].



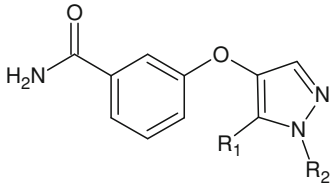
xiii



xiv

R_2 = NO_2, F, Cl, Br, H, CH_3, CH_3Cl

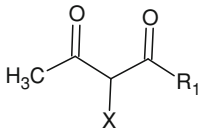
A number of pyrazole derivatives **(xv)** bearing structural features for a promising binding of therapeutically interesting enzymes, were prepared by Pellegrino et al. [19].



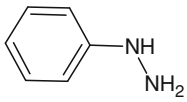
xv

R_1 = C_6H_5, BrC_6H_4, 4-$OCH_3C_6H_4$ **R_2** = H, C_6H_5

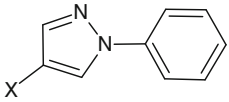
Poltshettiwar and Varma [20] utilized the nano-organocatalyst for the microwave-assisted pyrazole **(xviii)** synthesis. The key step involved the reaction of 1,3-diketones **(xvi)** with hydrazides **(xvii)**.



xvi



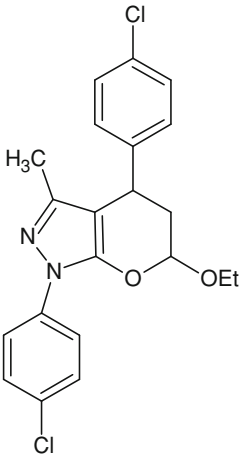
xvii



xviii

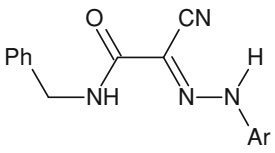
R_1 = Me, OEt **X** = H, Et, Cl

Another rapid protocol for the multicomponent microwave assisted organocatalyst Knoevenagel/hetero Diels–Alder reaction (DKHDA) for the synthesis of substituted 2,3-dihydropyran [2,3-c] pyrazoles **(xix)** has been developed by Radi et al. [21].

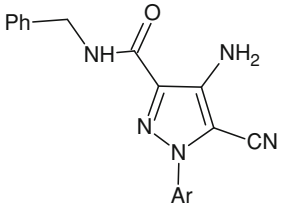


xix

Al-Zaydi [22] reported the synthesis of various pyrazole derivatives **(xxi)** by the reaction of arylhydrazones **(xx)** with chloroacetonitrile.



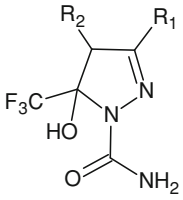
xx



xxi

Ar = C_6H_4-CO_2Me-o, $C_6H_4NO_2$

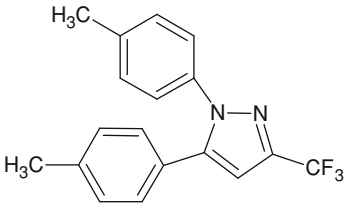
Sauzem et al. [23] demonstrated that the 5-trifluoromethyl-4,5-dihydro-1H-pyrazole scaffold **(xxii)** behaves like benzene bioisosteres, supplying novel analgesic and anti-inflammatory pyrazole derivatives. The target pyrazoles were obtained through a rapid one pot cyclocondensation reaction via microwave irradiation.



xxii

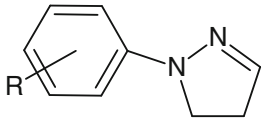
R_1 = H, Me, Et, Pr, i-Pr, t-Bu **R_2** = H, Me

The application of microwave heating to a silica-assisted solution-phase synthesis has been utilized by Humphries and Finefield [24] for an efficient two-step protocol for the preparation of pyrazoles **(xxiii)** from aryl methyl ketone and aryl hydrazine monomers.



xxiii

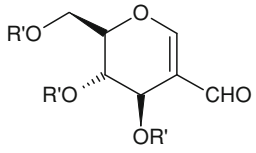
Ju and Varma [25] reported the direct synthesis of 4,5-dihydro-pyrazole **(xxiv)** via double-alkylation of hydrazines by alkyl dihalides in aqueous media under microwave irradiation conditions.



xxiv

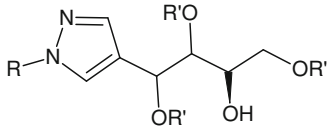
R = H, Me, Cl

A series of optically pure 4-substituted pyrazoles **(xxvi)** in good yields with high selectivities were obtained by Yadav et al. [26], following a condensation reaction between 2-formyl glycols **(xxv)** with arylhydrazines under solvent-free conditions.



xxv

R = Aryl, H



xxvi

R′ = Bn, Et, Me

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Chapter 7
Imidazoles

Abstract The importance of imidazoles in biological systems attracted great interest because of their chemical and biochemical characteristics. Even today, research in imidazole chemistry continues unabated. Compounds with an imidazole ring system have numerous pharmacological properties and play important roles in biochemical processes. The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole and its relatives, the benzodiazepine antagonist Flumazenil, the antineoplastic drug Dacarbazine, the antibiotic Metronidazole, the antiulcerative agent Cimetidine, the antihyperthyroid drug Methimazole, the prohormone Thyroliberin, the muscarinic receptor agonist Pilocarpine and the hypnotic agent Etomidate. In view the development of simpler and more convenient synthetic routes for preparing these heterocyclic systems have been achieved. This aspect has been dealt with in this chapter.

Keywords Imidazoles · Polycyclic derivatives · Poly (arylimidazole) · Polymer salt · Antitumor activity

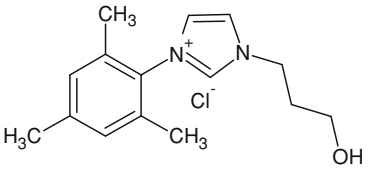
The importance of imidazoles in biological systems attracted great interest because of their chemical and biochemical characteristics. Even today, research in imidazole chemistry continues unabated. Compounds with an imidazole ring system have numerous pharmacological properties and play important roles in biochemical processes [1, 2]. The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole and its relatives, the benzodiazepine antagonist Flumazenil, the antineoplastic drug Dacarbazine, the antibiotic Metronidazole, the antiulcerative agent Cimetidine, the antihyperthyroid drug Methimazole, the prohormone Thyroliberin, the muscarinic receptor agonist Pilocarpine and the hypnotic agent Etomidate

Many substituted imidazoles are known as inhibitors of P38 MAP kinase, fungicides and herbicides, plant growth regulators, and therapeutic agents [3].

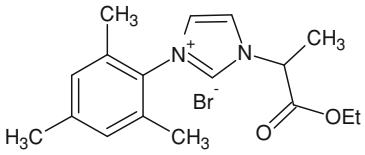
A. Rauf and N. N. Farshori, *Microwave-Induced Synthesis of Aromatic Heterocycles*, SpringerBriefs in Green Chemistry for Sustainability,
DOI: 10.1007/978-94-007-1485-4_7, © The Author(s) 2012

Several sydnone compounds are also associated with pharmacological activities, including antimicrobial, anti-inflammatory, analgesic and antipyretic properties [4–6]. In view there is a continued interest in the development of simpler and more convenient synthetic routes for preparing these heterocyclic systems.

Truscott et al. [7] gave the microwave assisted rapid and convenient access to the unsymmetrical N′-substituted N-mesitylimidazolium salts **(i, ii)**. These salts are an important precursors for the NHC (N-heterocyclic carbenes) used in the construction of metal-NHC complexes.

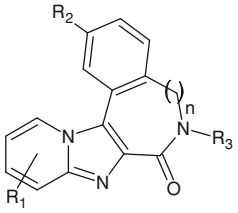


i



ii

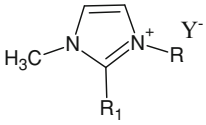
The Pd-catalyzed intramolecular arylation involving C (sp2)-H activation gave a library of fused pyridoimidazoquinolinones **(iii)**. The green synthesis afforded the polycyclic derivatives in good yields [8].



iii

R₁ = H, Me, Cl, OMe **R₂** = H, Me **R₃** = PMB, Bn, Boc **n** = 0,1

Aupoix et al. [9] gave an efficient, one-pot procedure for the synthesis of ionic liquids based on nitrogen-containing imidazolium heterocycles **(iv)** under green chemistry conditions.

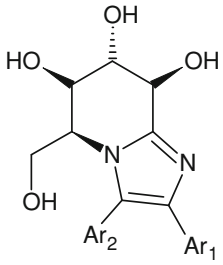


iv

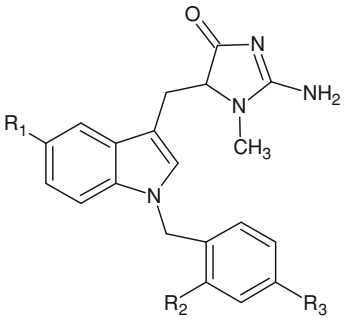
R = C_4H_9, C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{16}H_{33}$ **R₁** = H, Me **Y** = OTf, PF_6, BF_4, NTf_2

Two unprecedented one-pot synthetic protocols for the synthesis of imidazo[1,2-α]pyridine scaffolds **(v)** from carbohydrates have also been described by

Yadav and Awasthi [10]. Penthala et al. [11] synthesized a series of novel substituted (*Z*)-2-amino-5-(1-benzyl-1H-indol-3-yl)methylene-1-methyl-1H-imidazol-4(5H)-one **(vi)** analogs under microwave condition. The synthesized compounds when evaluated for their anticancer activity against a panel of 60 human cancer cell lines showed promising results.



v

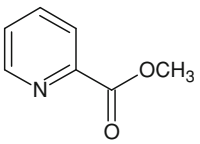


vi

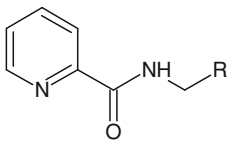
Ar$_1$ = C_6H_5, p-ClC_6H_4, p-$MeOC_6H_4$ **R$_1$** = H, Cl, Br, CH_3, OCH_3 **R$_2$** = H

Ar$_2$ = C_6H_5, p$MeOC_6H_4$ **R$_3$** = CN, NO_2, Cl, $COOCH_3$, F, OCH_3, CH_3

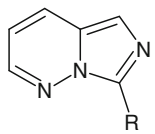
The 3-substituted-imidazo[1,5-α]pyridines **(ix)** were conveniently synthesized in a two step protocol from picolinic esters **(vii)** via the formation of picolinamides **(viii)** under microwave radiation by Aravapalli et al. [12]. Zhu et al. [13] used the ionic liquid 1,2,3-trimethyl-imidazole tetrafluroborate for the synthesis of ZnOHF nanabelts (NBs).



vii



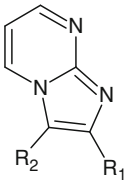
viii



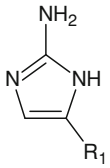
ix

R = Phenyl, 4-CF_3-phenyl, 4-CN-phenyl, 4-NMe_2-phenyl, 4-OMe-phenyl

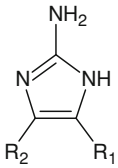
The microwave assisted hydrazinolysis of substituted imidazo[1,2-α]pyrimidine **(x)** gave way to mono **(xi)** and disubstituted **(xii)** 2-amino-1H-imidazoles [14].



x



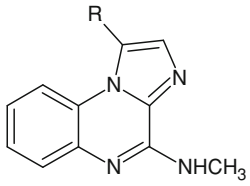
xi



xii

R_1 = Ph, p-MeOPh, p-FPh, p-MePh, p-NO_2Ph R_2 = p-ClPh, p-FPh, p-CF_3Ph, p-MeOPh

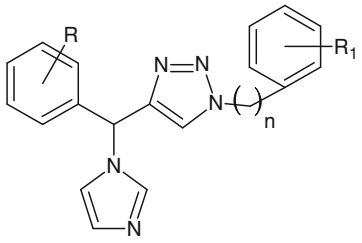
Deleuze-Masquefa et al. [15] showed that the microwave assisted bimolecular condensation of 2-imidazole carboxylic acid, followed by coupling with *ortho*-fluoroaniline and subsequent substitution on imidazole ring by Suzuki cross-coupling reaction gave the imidazo[1,2-α]quinoxaline **(xiii)** analogues in good yields. All the synthesized compounds showed high activities when evaluated for anti-tumor activities.



xiii

R = C_6H_5, 3-OCH_3-C_6H_4, 3-OH-C_6H_4, 3-Br-C_6H_4, C_6H_5-(CH_2)-

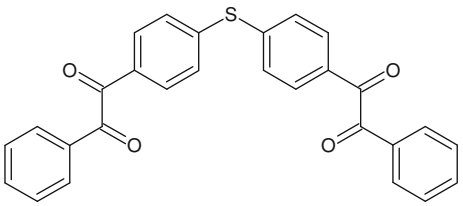
Various enantiomerically pure imidazole analogues **(xiv)** have been synthesized by Castagnolo et al. [16]. The synthesis involved the one-pot microwave synthesis of imidazole ring from a primary amine.



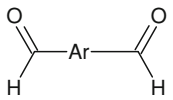
xiv

R = 4-F, 4-Br, 4-Cl R_1 = H, 4-Cl **n**=0, 1

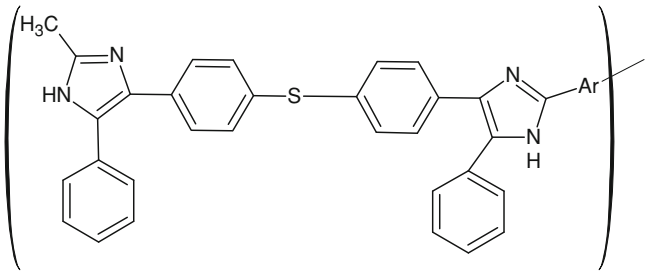
Various high molecular weight poly(arylimidazole) structures **(xvii)** have also been synthesized by Chauveau et al. [17]. The desired polymers were obtained by a one-pot polycondensation reaction involving a bis(α-diketone) **(xv)**, an aromatic dialdehyde **(xvi)** and ammonium acetate under microwave condition.



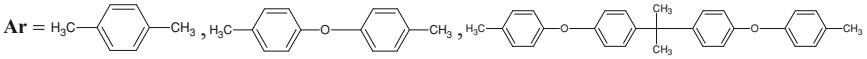
xv



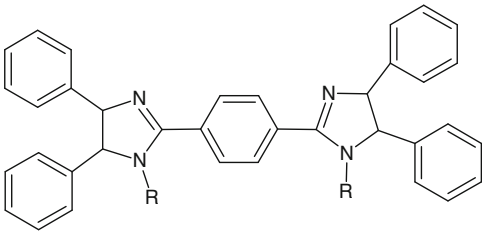
xvi



xvii



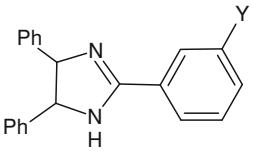
Pan et al. [18] synthesized the 1-alkyl-2,4-5-triphenylimidazole derivatives **(xviii)** using tetra-n-butylammonium bromide as a phase-transfer catalyst and determined their optical properties. This provided a convenient and efficient approach to the preparation of some useful dyes and pigments.



xviii

R = n-butyl, n-dodecyl

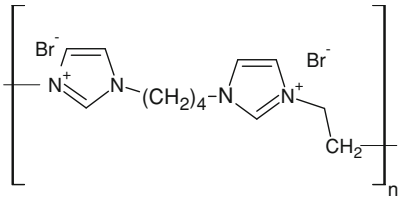
Various trisubstituted imidazoles **(xix)** have been synthesized in good yields by Shaabani et al. [19] via the condensation of 1,2-diketone or α-hydroxyketone or α-ketoxime with various aromatic aldehydes and ammonium acetate using a solid acid catalysis.



xix

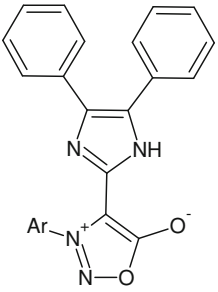
Y = 4-H, 4-CH_3, 4-OCH_3, 4-Cl, 4-Br, 2-Me

The imidazole polymer salt **(xx)** has also been synthesized to develop a high efficiency phase-transfer catalyst for multi-phase reactions [20].



xx

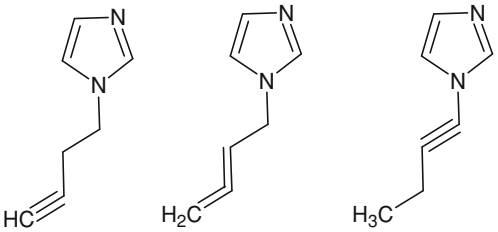
The microwave assisted synthesis of sydnonyl-substituted imidazoles **(xxi)** has also been given by Shih et al. [21]. This reaction which takes 1–3 days at high temperature under classical conditions is completed successfully within a few minutes under microwave irradiation.



xxi

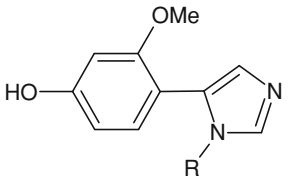
Ar = C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-$C_2H_5OC_6H_4$

Similarly, Perozo-Rondon et al. [22] gave the microwave enhanced synthesis of N-propargyl derivatives of imidazole **(xxii**, **xxiii**, **xxiv)** involving the Knoevenagel condensation reaction. The synthesized derivatives proved to be good fungicidal compounds.

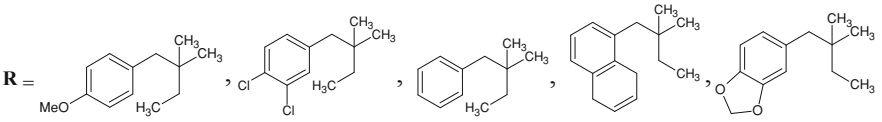


xxii **xxiii** **xxiv**

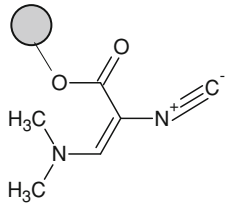
Samanta et al. [23] conveniently synthesized the 1,5-disubstituted imidazoles **(xxv)** on a polymeric support using base-promoted 1,3-dipolar cycloaddition reaction of *p*-toluenesulfonylmethyl isocyanide (TOSMIC) with immobilized imines under microwave irradiation.

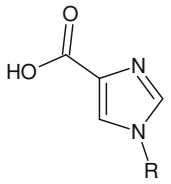


xxv

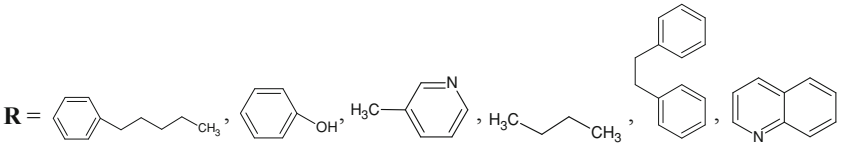


Henkel [24] used the novel 3-*N*,*N*(dimethylamino)-isocyanoacrylate-wang resin **(xxvi)** for the synthesis of imidazole-4-carboxylic acids **(xxvii)** in a microwave reaction condition.

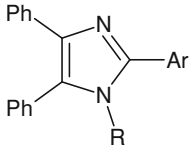




xxvi **xxvii**



Tetrasubstituted imidazoles **(xxviii)** were also obtained in high yields by a one-pot, three-component condensation of benzyl, benzonitrile derivatives and 1° amines on the surface of silica gel under solvent free microwave condition [2].



xxviii

Ar = Ph, 4-$CH_3C_6H_4$, 3-BrC_6H_4, 3-$NH_2C_6H_6$ **R** = $PhCH_2$, $PhCH(CH_2)$, C_2H_5, iso-C_4H_9

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Chapter 8
Triazoles

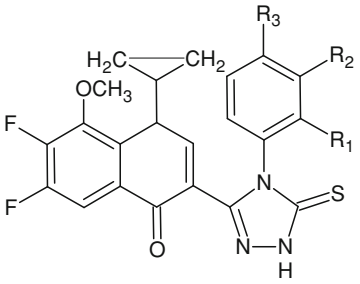
Abstract Triazole and its derivatives belong to a class of exceptionally active compounds possessing a wide spectrum of chemotherapeutic activities, including anticonvulsant, antimicrobial, antihypertensive, analgesic, antiviral, antioxidant, anti-inflammatory, antitumor and anti-HIV activity. In addition, it was reported that compounds having triazole moieties, such as vorozole, letrozole and anastrazole appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer. Apart from their pharmacological significance triazole derivatives exhibit interesting chemical properties. The ability of triazoles to form a bridge between metal ions makes such ligands very important for magnetochemical applications. Some complexes containing substituted triazole ligands have potential uses as optical sensors or molecular-based memory devices. The synthesis of this heterocyclic moiety under microwave conditions is described in this chapter.

Keywords 1,2,4/1,2,3-Triazoles · CuAAC · Suzuki coupling · 1,3-Dipolar cycloaddition · Antimicrobial activity

Triazole and its derivatives belong to a class of exceptionally active compounds possessing a wide spectrum of chemotherapeutic activities, including anticonvulsant [1], antimicrobial [2], antihypertensive [3], analgesic [4], antiviral [5], antioxidant [6], anti-inflammatory [7], antitumor [8] and anti-HIV activity [9]. In addition, it was reported that compounds having triazole moieties, such as vorozole, letrozole and anastrazole appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer [10]. Apart from their pharmacological significance, triazole derivatives exhibit interesting chemical properties. The ability of triazoles to form a bridge between metal ions makes such ligands very important for magnetochemical applications [11]. Some complexes containing substituted triazole ligands have potential uses as optical sensors or molecular-based memory devices [12].

A. Rauf and N. N. Farshori, *Microwave-Induced Synthesis of Aromatic Heterocycles*, SpringerBriefs in Green Chemistry for Sustainability,
DOI: 10.1007/978-94-007-1485-4_8, © The Author(s) 2012

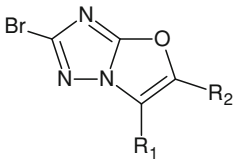
A series of fluorine-containing triazole **(i)** have been synthesized by the treatment of thiosemicarbazides with 1% NaOH by green techniques [13].



i

$\mathbf{R_1}$ = H, CH_3 $\mathbf{R_2}$ = H, CH_3 $\mathbf{R_3}$ = H, Cl, OCH_3

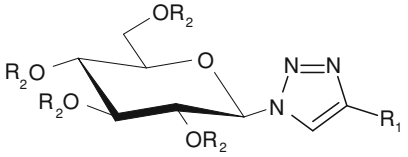
Ball et al. [14] developed a one-pot expedient microwave approach for the synthesis of novel [1,3]oxazolo[3,2,b][1,2,4]triazoles **(ii)** via a tandem alkylation/cyclisation reaction of 3-bromo-1,2,4-triazoles and α-haloketone via an intermediate enolate.



ii

$\mathbf{R_1}$ = CH_3, COOEt, Ph, CF_3 $\mathbf{R_2}$ = CH_2CH_3, $COCH_3$, $COOCH_3$

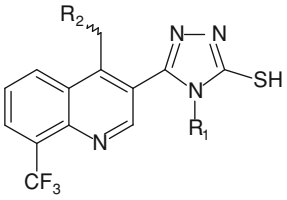
The Cu^1-catalysed azide alkyne 1,3-dipolar cycloaddition (CuAAC) click chemistry has also been used to synthesize a library of α,β-D-glucopyranosyl triazoles **(iii)**. The synthesized triazoles proved to be potential glycosidase inhibitors [15].



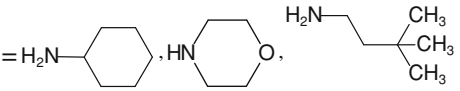
iii

$\mathbf{R_1}$ = CH_2OCHPh_2, Ph, CH_2OH, COOMe, COOH $\mathbf{R_2}$ = Ac, H

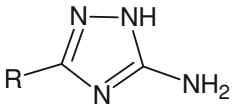
Eswaran et al. [16] reported the successful synthesis of new 5-(4-amino substituted-8-(trifluoromethyl)quinolin-3-yl)-4-(un)substituted phenyl-4*H*-1,2,4-triazole-3-thiols **(iv)** carrying biologically active groups.



iv

$\mathbf{R_1}$ = CH_2Ph, Ph, CH_2CH_2OMe $\mathbf{R_2}$ = 

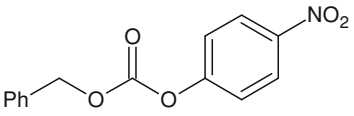
Dolzhenko [17] gave a catalyst free aqueous medium synthesis of 3(5)-amino-5(3)-(het)aryl-1,2,4-triazole **(v)** under microwave condition.



V

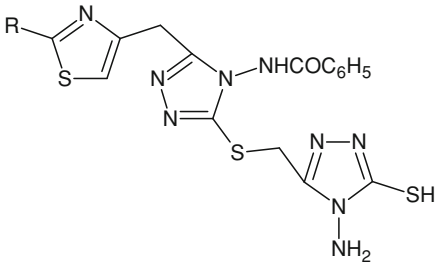
R = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 2-furyl, 3-pyridyl

Meng and Kung [18] also exploited a robust, regioselective synthetic approach to 3-amino-1,2,4-triazoles from commercially available carbonic acid benzyl ester 4-nitrophenyl ester **(vi)**.



vi

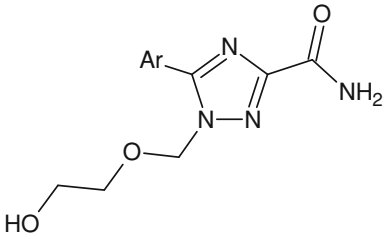
Shiradkar et al. [19] reported the synthesis of clubbed thiazolyl triazole derivatives **(vii)** starting from ethyl acetoacetate, by microwave organic reaction enhanced method (MORE). The synthesized triazoles showed promising antimicrobial and antimycobacterial activities.



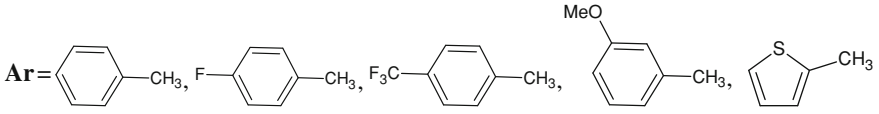
vii

R = $NHCOCH_2Cl$, $NHCOCl_3$, $NHCOC_6H_5$, $NHCH_2CH_2COOH$

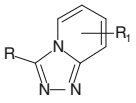
5-aryltriazole acylonucleosides **(viii)** bearing various aromatic groups on the triazole ring have been obtained by a Suzuki coupling reaction. The coupling reaction was significantly promoted in aqueous medium under microwave conditions to yield the desired triazole derivatives [20].



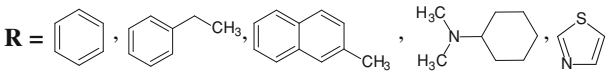
viii



Wang et al. [21] showed that the triazolopyridine derivatives **(ix)** can be synthesized from a variety of carboxylic acids with 2-hydrazinopyridines in one simple step by using the commercially available PS-PPh_3 resin with microwave heating.



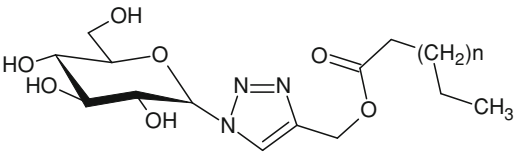
ix



R_1 = H, NO_2, CF_3, Cl, CH_3

An expedient synthesis of 3,5-disubstituted-1,2,4-triazoles proceeding by the direct reaction of a nitrile and a hydrazide in presence of catalyst K_2CO_3 in n-BuOH has been developed by Yeung et al. [22]. A diverse range of functionality and heterocycles were tolerated under the reaction conditions. A quick preparation of symmetrically 3,5-disubstituted-4-amino-1,2,4-triazoles, under microwave condition is also reported by Bentiss et al. [23].

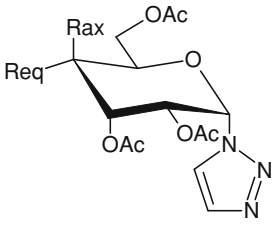
Song et al. [24] gave an effective preparation of a series of triazole-linked ester-type glycolipids **(x)** via a two-step sequence involving microwave accelerated click chemistry and debenzylation.



x

n = 1, 3, 5, 8, 9, 10, 11, 12, 14

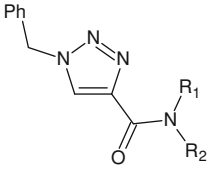
A number of glycosyl-1*H*-1,2,3-triazoles **(xi)** were prepared by the reaction of the corresponding azides with vinyl acetate under microwave irradiation [25].



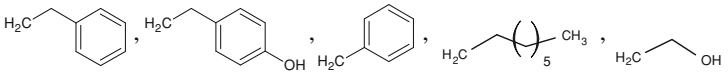
xi

Rax = H, OAc **Req** = H, OAc

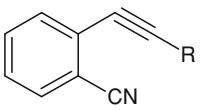
Yang et al. [26] gave a convenient sequential one-pot protocol for the synthesis of C-carbamoyl-1,2,3-triazoles **(xii)** from alkyl bromide.



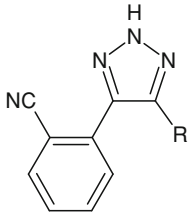
xii

R1 = H **R2** = 

The treatment of 2-alkynylbenzonitriles **(xiii)** with sodium azide in DMSO also gave 4,5-disubstituted-2*H*-1,2,3-triazoles **(xiv)** [27].



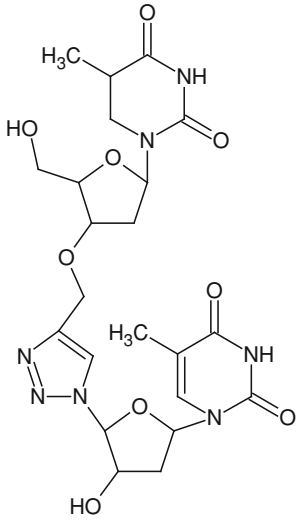
xiii



xiv

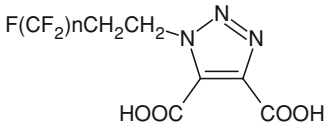
R = C_6H_5, p-$NO_2C_6H_4$, p-$CF_3C_6H_4$, p-MeC_6H_4, 2-thienyl, n-butyl, tert-butyl

The triazole-linked 3′-5′ thymidine dimmer **(xv)** has been synthesized by utilizing the 1,3-dipolar cycloaddition reaction under microwave irradiation [28].



xv

Mayot et al. [29] synthesized a series of fluoroalkylated amphiphilic 1,2,3-triazoles **(xvi)** by the 1,3-dipolar cycloaddition of 2-perfluoroalkyl-ethyl-azides by heating in microwave conditions.



xvi

n = 4, 6, 8

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Chapter 9
Triazines

Abstract Triazines are a representative class of heterocyclic compounds with a wide variety of interesting properties which are used in medicine and agriculture. It has been associated with diverse pharmacological activities such as hypertension and inhibition of platelets, antileukemic, anti-inflammatory and potent neuroprotective agents. The triazine moiety is a structural element in antimalarial, anticancer, antifungal, anticonvulsant, antibacterial, and antiviral compounds. Certain compounds containing a triazine nucleus have been reported to possess pesticidal, neuropharmacological, analgesic and antidepressant properties. The wide ranging biological activity associated with triazine derivatives, both naturally occurring and synthetic ensures that the synthesis of this important ring system remains a topic of current interest. Various methods for the preparation of these compounds have been reported. A few of these methods have been discussed in this chapter.

Keywords 1,2,4/1,3,5-Triazines · CTF/Fe_2O_3 composite · CDR's · Cytotoxicity · Antimicrobial activity

Triazines are a representative class of heterocyclic compounds with a wide variety of interesting properties which are used in medicine and agriculture [1, 2]. It has been associated with diverse pharmacological activities such as hypertension and inhibition of platelets [3], antileukemic [4], anti-inflammatory [5] and potent neuroprotective agents [6]. The triazine moiety is a structural element in antimalarial [7], anticancer [8], antifungal [9], anticonvulsant [10], antibacterial [11], and antiviral [12] compounds. Certain compounds containing a triazine nucleus have been reported to possess pesticidal [13], neuropharmacological [14], analgesic and antidepressant [15] properties. Some triazine derivatives are used for the determination of metal ions and as dyes [3]. *N*-Methyl derivatives of triazines are the naturally occurring antibiotics fervenulin (planomycin), toxoflavin (xanthothricin) and reumycin.

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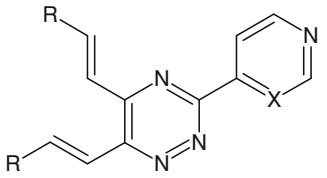
The wide ranging biological activity associated with triazine derivatives, both naturally occurring and synthetic ensures that the synthesis of this important ring system remains a topic of current interest. Various methods for the preparation of these compounds have been reported.

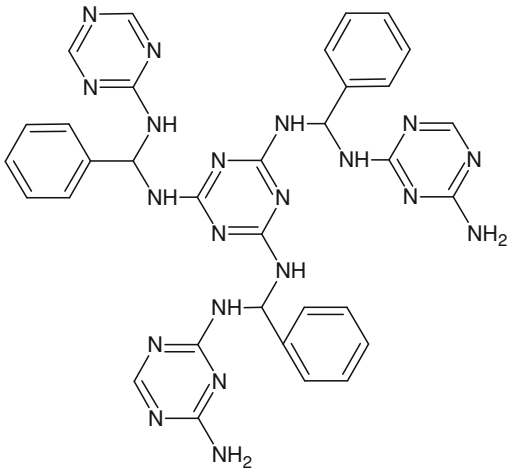
Thirumurugan and Perumal [16] effectively synthesized bisaryl-3-pyridinyl-1,2,4-triazine derivative **(i)** following the microwave condensation of cinnamils with pyridine carboxtrisamidrazone in methanol. The triazine derivatives were obtained in good yields (85–66%) and showed good fluorescent properties when photochemical analysis was carried out.



i

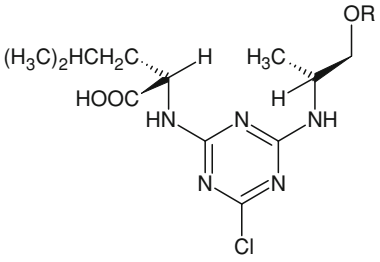
The microwave enhanced synthesis of magnetic porous carbonaceous polymeric materials CTF/Fe_2O_3 composite (CTF = covalent triazine based framework) has been given Zhang et al. [17]. The synthesized composite finds great application in the fast separation of organic dyes from aqueous solutions.

Yang et al. [18] synthesized the melamine based porous polymer networks **(ii)** by the reaction of melamine, terephthaldehyde and DMSO under microwave condition. The polymer finds its application for the removal of aqueous mercury ions.



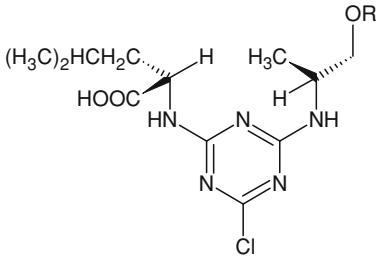
ii

A new series of chiral derivatizing reagents (CDRs) consisting of 4-dichloro-*s*-triazine (DCT) and six monochloro-*s*-triazine (MCT) reagents have been prepared by Bhushan and Dixit [19]. These CDRs on reaction under microwave conditions result in the formation of diastereomers of (*R,S*) mexiletine **(iii, v).** The same procedure was adapted for the synthesis of diastereomers of (*R,S*)-baclofen [20].



iii

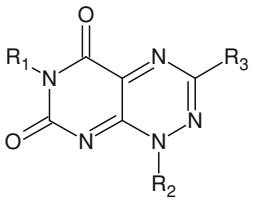
R-configuration



iv

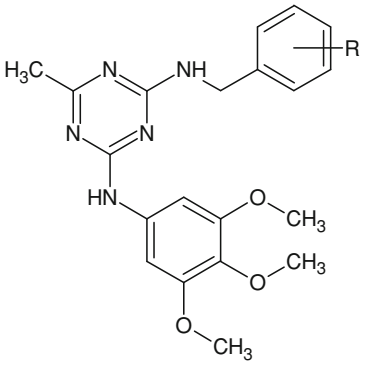
S-configuration

Todorovic et al. [21] gave the synthesis of a library of 3-aryl-pyrimido [5,4-e] [1,2,4]-triazine-5,7-(1H,6H)-dione **(v)** following microwave approach. The use of microwave irradiation allowed the rapid reaction times and good yields of products. It also avoids the use of metal salts.



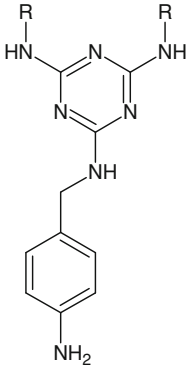
v

The practical preparation of novel 2-(arylmethyl) amino-4-arylamine-6-alkyl-1,3,5-triazines **(vi)** from the microwave assisted reaction of easily accessible dicyanidiamide and arylamines has also been described [22].

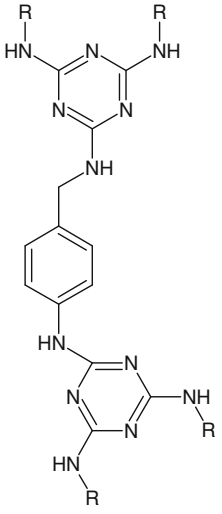


vi

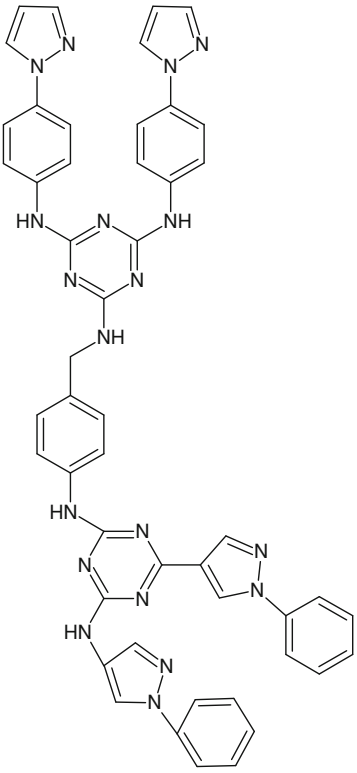
Various mono- and bistriazines have been synthesized by Moral et al. [23] under microwave conditions. The use of a diamine bearing amino groups of different reactivities, selectively gave monotriazines **(vii),** bistriazines with identical substituents **(viii)** and differently substituted bistriazines **(ix)**. The newly synthesized bistriazines showed promising applications in supramolecular chemistry based on hydrogen bonds and/or complexation with metals. They are also expected to show interesting fluorescence properties by complexation with cyanuric and barbituric acid derivatives.



vii

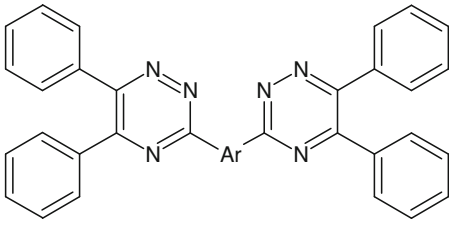


viii



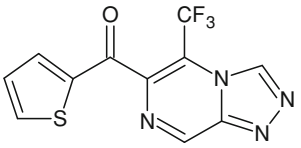
ix

Sun et al. [24] synthesized the nitrogen containing heterocyclic chromophores based on 1,2,4-triazine **(x)** under microwave irradiation.

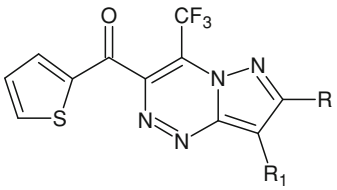


x

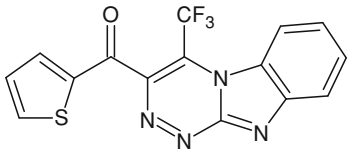
The coupling of the 4,4,4-trifluoro-1-(thien-2-yl) butane-1,3-dione with azole diazonium salts gives the pyrazolo [5,1-c] triazine **(xi)**, benzimidazo [5-1-c] 1,2,4-triazine **(xii)** and triazolo [3,3-c] 1,2,4-triazine **(xiii)** derivatives incorporating trifluoromethyl group [25].



xi

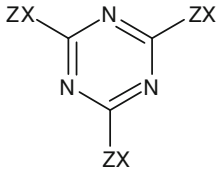


xii



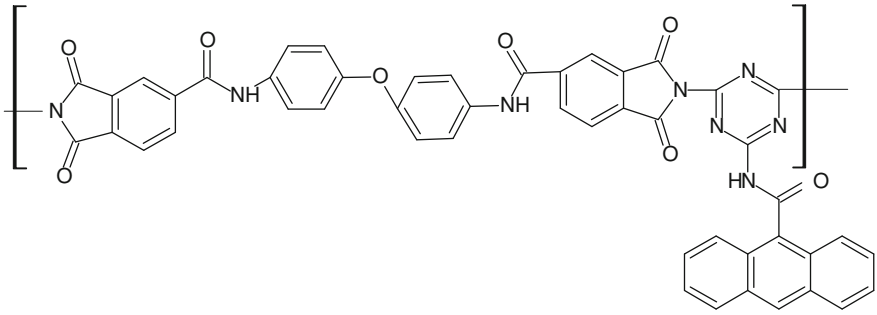
xiii

Arya and Dandia [26] presented the HY zeolite promoted, environmentally benign solvent free synthesis of 2,4,6-trisubstituted-1,3,5-triazines **(xiv)** under microwave irradiation. The synthesized derivatives also showed promising activities when screened for phototoxicity and cytotoxic activities against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes.



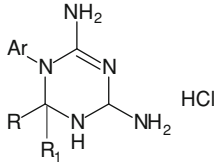
xiv

A novel photoactive thermally stable polymer **(xv)** containing the triazine moiety has been synthesized by Khoee and Zamani [27] by the reaction of *N,N*-(4,4′-oxy bis (4,1-phenylene))-bis-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamide) and *N*-(4,6-diamino-1,3,5-triazin-2-yl) anthracene-9-carboxamide in presence of a small amount of *o*-cresol as a solvent under microwave condition.



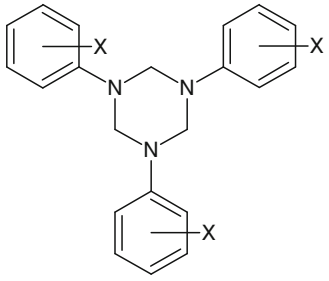
xv

Kidwai et al. [28] synthesized the 1-aryl-4,6-diamino-1,2-dihydrotriazine by reacting the suitable aldehyde, cyanoguanidine **(xvi)** and an aromatic amine with condensed HCl under microwave irradiation. The compounds showed good results when tested for their in-vitro antimicrobial activity against both sensitive and resistant *Plasmodium falciporum* strains.



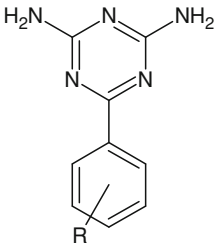
xvi

Dandia et al. [29] gave the economic, ecofriendly, facile, one pot synthesis of fluorinated 1,3,5-triaryl hexahydro-1,3,5-triazine **(xvii)** following the condensation of fluorinated amines with formaldehyde under microwave irradiation in aqueous medium. The target triazines were obtained in excellent yields (98–99%) and showed good activity against the selected fungal strains of *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici.*



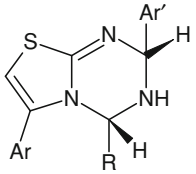
xvii

The green synthesis of 6-aryl-2,4-diamino-1,3,5-triazines **(xviii)** from corresponding aryl-nitriles and dicyano diamide using computer controlled microwave irradiation in conjugation with a green solvent [bmim] [PF_6] has also been achieved [30].



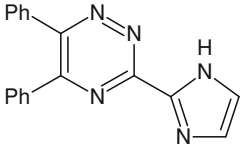
xviii

Yadav and Kapoor [31] investigated the potential of microwaves to accelerate the 3cc reaction between thiazole schiff's base, ammonium acetate and an aldose to diastereoselectively yield the new acyclic *C*-nucleosides incorporating the thiazolo-*s*-triazine **(xix)** structure as the nucleobase.



xix

Zhao et al. [32] applied the microwaves for the synthesis of diverse 3,5,6-trisubstituted-1,2,4-triazines **(xx)** in excellent yields and purity. The synthetic protocol involved the reaction of benzyl and imidazoyl acyl hydrazide in presence of ammonium acetate and glacial HOAc.



xx

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Chapter 10
Benzimidazoles, Benzothiazoles and Benzoxazoles

Abstract Benzimidazoles, benzothiazoles and benzooxazoles are privileged structural units not only in the pharmaceutical industry but also in several other fields such as agricultural, electronic, and polymer chemistry. This ring system is present in numerous antioxidant, antiparasitic, antihelmintics, antiproliferative, anti-HIV, anticonvulsant, anti-inflammatory, antihypertensive, antineoplastic and antitrichinellosis activities. Owing to the immense importance of benzimidazoles, efforts have been made from time to time to generate various derivatives of these compounds. These methods have been well described in this Chapter.

Keywords Benzimidazoles · Benzthiazoles · Banzoxazoles · Solid-phase synthesis · Antitumor activity

10.1 Benzimidazoles

Benzimidazoles are privileged structural units not only in the pharmaceutical industry but also in several other fields such as agricultural, electronic, and polymer chemistry [1, 2]. Specifically this nucleus is a constituent of vitamin-B_{12}. This ring system is present in numerous antioxidant [3], antiparasitic [4], anti-helmintics [5], antiproliferative [6], anti-HIV [7], anticonvulsant [8], anti-inflammatory [9], antihypertensive [10], antineoplastic [11] and antitrichinellosis [12] activities. Owing to the immense importance of benzimidazoles, efforts have been made from time to time to generate various derivatives of these compounds.

Cheng-Ting et al. [13] developed a simple and efficient method for the synthesis of benzimidazole linked quinoxalinones **(i)** on soluble polymer support using microwave conditions. The key steps involved in the implemented linear synthesis are the acid catalyzed condensation of 4-fluoro-3-nitrobenzoic acid with polymer

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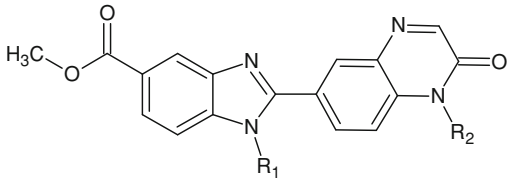
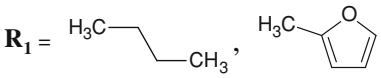
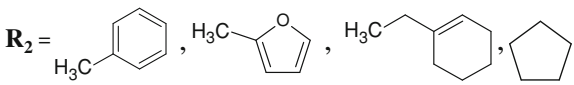
immobilized *o*-phenylenediamine, *ipso*-fluoro nucleophillic substitution with various primary amines and finally the cyclization with acetyl chloride.

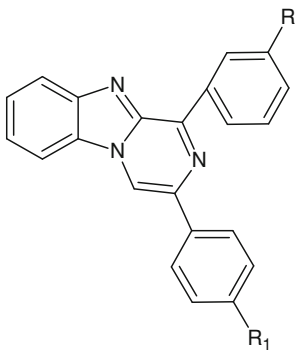


i





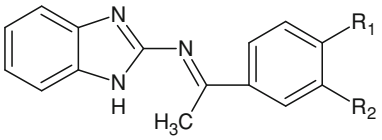
The synthesis of 1,3-diarylpyrazino[1,2-a]benzimidazole derivatives **(ii),** applying microwave irradiation as the reaction condition, has been achieved Demirayak et al. [14]. The new benzimidazole derivatives were obtained in good yields (65-86%) and were tested in vitro against sixty human tumor cell lines derived from nine neoplastic diseases.



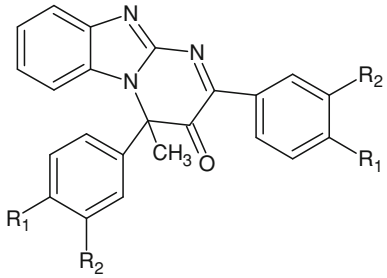
ii

R = H, OMe, Cl **R₁** = H, OMe, F, Cl, Me

Benzimidazole schiff bases **(iii)** and 3-oxo-primido [1,2-α] benzimidazole **(iv)** have been generated in excellent yields by Neochoritis et al. [15]. The one-step sequence involved the reaction of 2-aminobenzimidazole under green chemistry conditions.



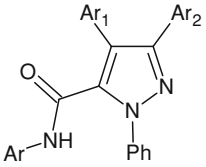
iii



iv

R_1 = H, Me, OMe, Cl, Br, 1-Naphthyl **R_2** = H, Me, OMe, Br

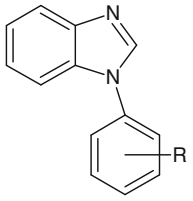
Abdel-Aziz et al. [16] reported the regioselective 1,3-dipolar cycloaddition of nitrilimines with 2-(4-arylidene)-thiazolo-[3,2-a]-benzimidazole-3-(2H)-ones to afford the corresponding pyrazoylbenzimidazole **(v).** The pyrazolylbenzimidazoles were also examined for their anti-tumor activities against two tumor cell lines, Hep-2 and colon CaCo-2 and encouraging results were obtained.



v

Ar = Ph, 4-Me-C_6H_4 **Ar_1** = Ph, 4-Cl-C_6H_4 **Ar_2** = Ph, 4-Cl-C_6H_4

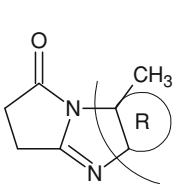
The utility of microwaves in the copper catalysed protocol for N-arylation using high molecular weight poly(ethylene glycol) (PEG_{3400}) as a solvent was explored by Colacino et al. [17] for accessing the N-arylated benzimidazole **(vi)** in presence of cuprous oxide, cesium carbonate and PEG_{3400} under microwave activation, with no supplementary ligands.



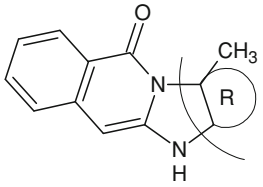
vi

R = 4-CN, 4-NO_2, 4-OMe, 4-Me

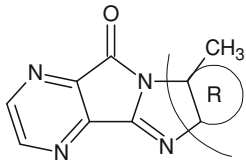
Sondhi et al. [18] reported the preparation of various tricyclic and tetracyclic benzimidazole derivatives **(vii, viii, ix)** in high yields and shorter reaction time by employing the microwave as the reaction condition. All the synthesized compounds showed prominent anti-inflammatory and anti-cancer activities.



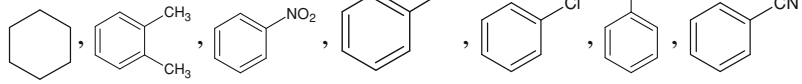
vii



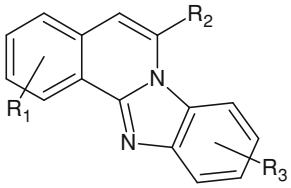
viii



ix

R = 

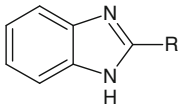
Okamoto et al. [19] described the direct synthesis of the benzimidazo [2,1-a] isoquinoline **(x)** ring system by a microwave-accelerated tandem process in which a sonogashira coupling, 5-endocyclization, oxidative aromatization and 6-endo cyclization can be performed in a single synthetic operation.



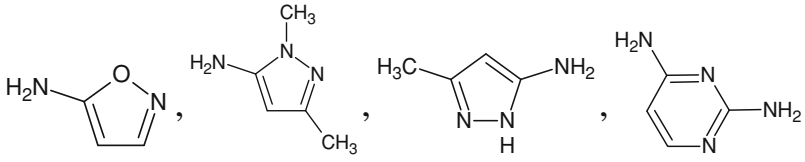
x

R_1 = H, 4-Me, 5-F **R_2** = Ph, p-Tol **R_3** = H, Me

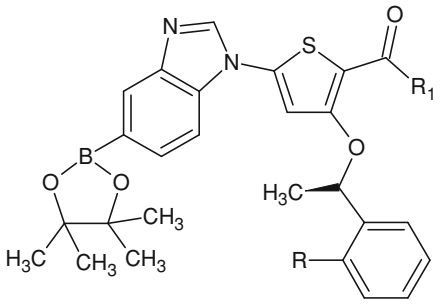
A one-pot microwave-assisted relay reaction for the synthesis of 2-substituted benzimidazoles **(xi)** have been reported by Pattabiraman et al. [20]. The products were obtained in good yields and the reaction times were significantly reduced.



xi

R = 

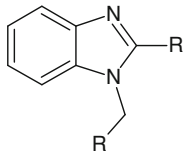
Rheault et al. [21] accessed a variety of heteroaryl linked benzimidazole **(xii)** derivatives following a convenient and mild microwave-assisted boronate ester formation.



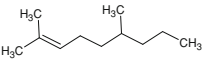
xii

R = Cl, CF_3 **R₁** = OMe, NH_2

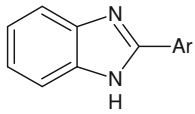
Jacob et al. [22] presented an improved green solvent free methodology for the selective synthesis of 1,2-disubstituted benzimidazoles **(xiii)** by the condensation of *o*-phenylenediamine and aldehydes using solid-supported catalyst ($SiO_2/ZnCl_2$).



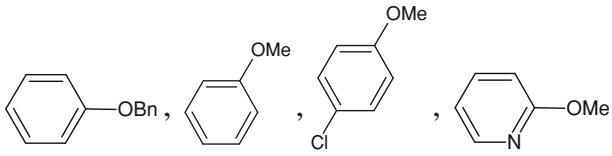
xiii

R = C_6H_5, C_3H_7, C_4H_9, $3CH_3C_6H_5$, $4CH_3OC_6H_5$, $2CH_3OC_6H_5$, 2-furyl, 

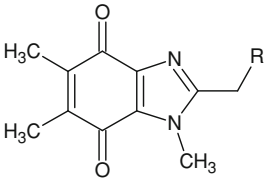
Savall et al. [23] reported a simple and efficient method for the direct synthesis of unprotected 2-aryl benzimidazoles **(xiv)** using microwave-mediated Suzuki–Miyaura cross coupling of readily available trifluoroborates and 2-chlorobenzimidazoles.



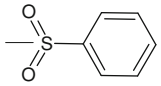
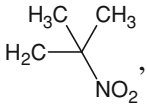
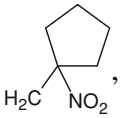
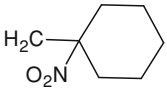
xiv

Ar = 

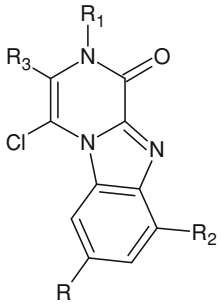
Various new benzimidazole-4,1-diones **(xv)** substituted at 2-position were synthesized via a microwave assisted reaction by Gellis et al. [24]. Their cytotoxicity has been evaluated on the colon, breast and lung cancer cell lines and good results were observed comparable to that of mitomycin C.



xvi

R = Cl, Br,  ,  ,  , 

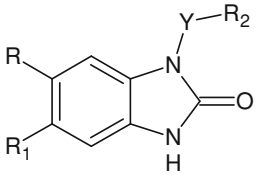
Alen et al. [25] applied the microwave assisted Buchwald-Hartwig type cyclization reaction for the synthesis of substituted pyrazino-[1,2-a]-benzimidazole-1(2H)-ones **(xvi)** starting from easily accessible dichloropyrazinones.



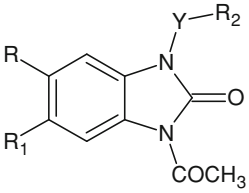
xvi

R = H, Me, F, Cl **R_1** = PMB, Ph **R_2** = H, Me, Cl, F **R_3** = H, Me, Ph

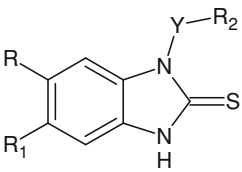
A series of novel N-substituted-1,3-dihydro-2H-benzimidazol-2-ones **(xvii, xviii, xix)** were synthesized and proved to be potent non-nucleoside reverse transcriptase inhibitors by Monforte et al. [26].



xvii



xviii

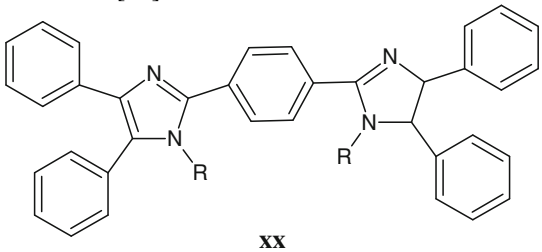


xix

R = Cl, CH_3, CF_3 **R_2** = 2,6-difluorophenyl

R_1 = H, F **Y** = CH_2, SO_2

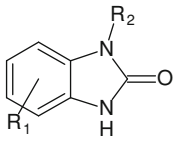
The alkylation reaction of corresponding 2,4,5-triphenylimidazole **(xx)** derivatives with alkyl bromide using tetra-n-butylammonium bromide as phase-transfer catalyst in presence of 50% NaOH in butanone yield various 1-alkyl-2,4,5-triphenylimidazole derivatives [27].



xx

R = n-butyl

Xu and Xong [28] developed a microwave-assisted tracer rapid synthesis of benzimidazoles **(xxi)** on a polymer support. The arylation of benzylammonia, followed by treatment with N-chlorosulfonyl isocyanate and subsequent hydrolysis gave primary ureas. The Pd-catalysed cyclization of resin bound primary ureas followed by cleavage with TFA-H_2O yielded the desired product in good yield and high purities.

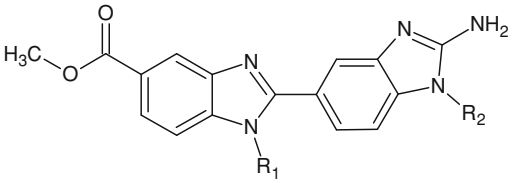


xxi

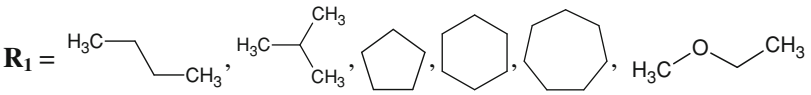
R_1 = 1-chloro-2-fluorobenzene, 2-chloro-5-fluoro-4 (trifluoromethyl) benzene, 3-chloro-2-fluorobenzonitrile

R_2 = Bn, i-Pr, Allyl, Me, i-Bu

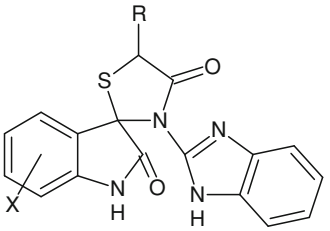
Wu and Sun [29] applied the single-mode microwave irradiation technique for the synthesis of specifically functionalized bis-benzimidazole **(xxii)** for potential DNA minor groove recognition study.



xxii



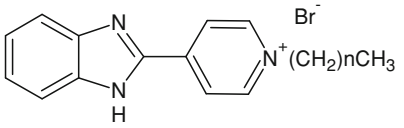
Various benzimidazolyl spiro[indole-thiazolidinones] **(xxiii)** have been synthesized following a three-component regioselective one-pot cyclocondensation strategy by Dandia et al. [30].



xxiii

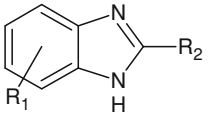
R = CH_3 **X** = 5-F, H, 5,7-diCH_3, 5-CH_3, 5-Br, 5-Cl

Yu et al. [31] gave the simple and microwave assisted synthesis of pyridinium salts **(xxiv)** consisting of long alkyl chains and benzimidazole moiety as a blue fluorescent gelators.



xxiv

Vanvliet et al. [32] developed a green, simple, one-pot procedure for the synthesis of 2-substituted benzimidazoles **(xxv)** directly from 2-nitroanilines.

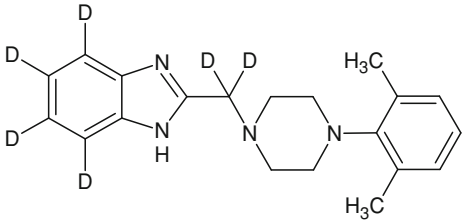


xxv

R_1 = H, 4,5-Dimethyl, 5-CH_3, 5-OCH_3, 5-COOH, 5-CN

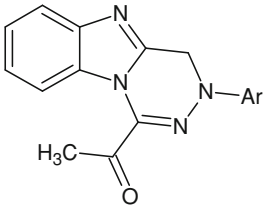
R_2 = H, CH_3, CF_3

Vaidyanathan and Surber [33] gave the synthesis of ^{2}H-substituted benzimidazoles **(xxvi)** by a hydrogen deuterium exchange reaction, mediated by microwaves.

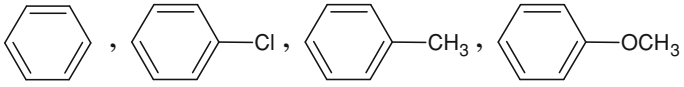


xxvi

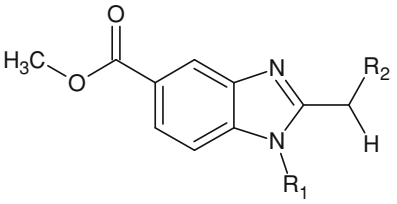
Highly functionalized tricyclic benzimidazole system **(xxvii)** has been synthesized under solvent-free microwave condition by Abdel-Jalil et al. [34].



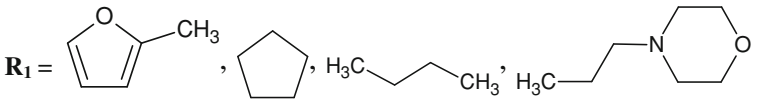
xxvii

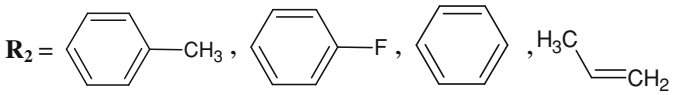
Ar = 

Su et al. [35] gave the mercury (II)-catalyzed liquid phase synthesis of 1,2-disubstituted benzimidazoles **(xxviii)** by utilizing S_NAr reactions, reduction and cyclization reaction. Tbe yield of the product ranged between 73–90%.

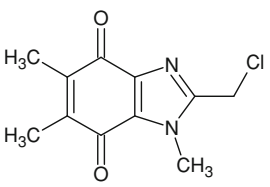


xxviii

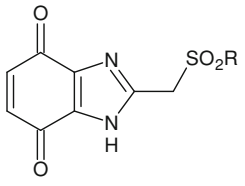




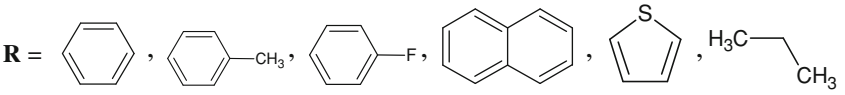
Bayatah et al. [36] efficiently synthesized the 2-substituted benzimidazole-4, 7-diones **(xxx)**. The intermediate 2-chloromethyl-1,5,6-trimethylbenzimidazole-4,7-dione **(xxix)** served as a point of departure for the synthesis of desired products.



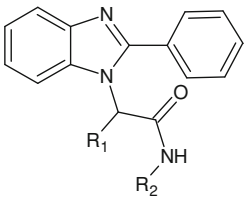
xxix



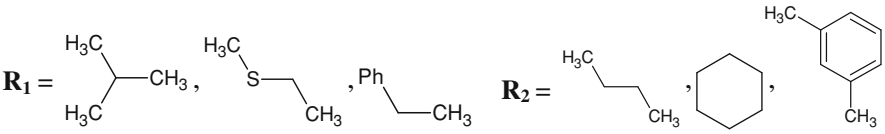
xxx



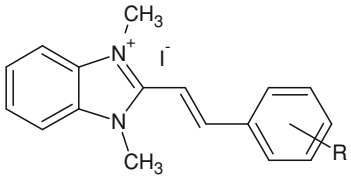
Zhang and Tempest [37] showed that the incorporation of microwave technology of an Ugi/de-BOC/cyclization strategy for the synthesis of substituted benzimidazoles **(xxxi).**



xxxi



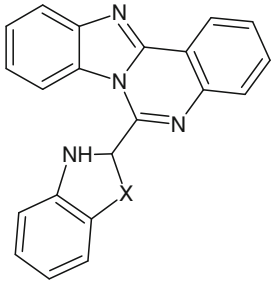
The 1,3-dimethyl-2-substituted styryl benzimidazolium salts **(xxxii),** a useful hemocyanine dyes have been synthesized by the solvent free microwave assisted condensation of 1,2,3-trimethyl benzimidazole salts with aromatic aldehydes in the presence of piperidine [38].



xxxii

R = p-N$(CH_3)_2$, p-OH, p-OCH_3, p-CH_3, p-H, m-NO_2, p-NO_2

Frere et al. [39] extended the microwave technology to the condensation reaction of diamines and 2-cyanobenzthiazoles, to obtain the benzimidazo-[1,2,c]-quinazolines **(xxxiii)** with potential pharmaceutical value.



xxxiii

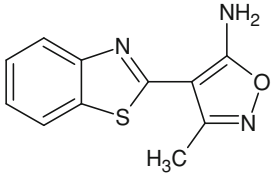
X = O, S

10.2 Benzothiazoles

2-Substituted benzothiazoles constitute an important class of compounds for medicinal, agricultural, and organic chemists. The benzothiazole-moiety can be found as a common substructure in a large number of compounds with a wide range of biological activities [40–42]. These compounds possess antitumor, antiviral, antimicrobial, and antiglutamate properties. Some of these compounds have been widely used in agriculture. For example, Bentaluron, Chlobenthiazone, and TCMTB, which have been used for many years, are commercial fungicides belonging to benzothiazole derivatives. 2-Benzothiazole thioether derivatives possess anticandious, antimicrobacterial, photosynthesis-inhibiting, fungicidal, insecticidal, and herbicidal properties [43–46].

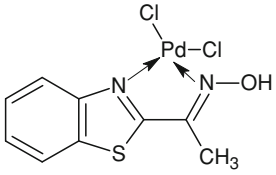
Benzothiazole is a privileged bicyclic ring system [47]. Due to their potent antitumour activity [48] and other important pharmaceutical utilities [49–52] the synthesis of these compounds is of considerable interests [53].

Pattabiraman et al. [54] synthesized the 2-substituted benzothiazoles **(xxxiv)** from inexpensive, commercially available reagent (2-benzthiazole acetonitrile) via a one-pot microwave assisted relay reaction.



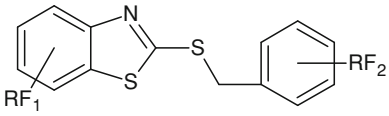
xxxiv

The catalytic activity of benzothiazole-oxime-based Pd (II)-complexes **(xxxv)** was evaluated in Suzuki–Miyaura and Heck-Mizoroki C–C cross coupling reactions of aryl bromides and chlorides with aryl boronic acid and olefins under microwave conditions in water was studied by Dawood [55].



xxxv

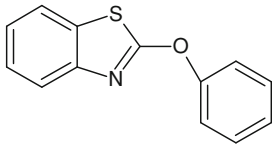
Huang and Yang [56] described for the first time the microwave assisted, one pot synthesis of polyfluorinated 2-benzylthiobenzothiazole derivatives **(xxxvi)** from readily available starting materials.



xxxvi

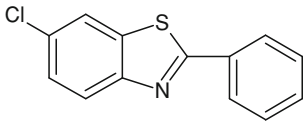
RF_1 = 4-F, 5-F, 6,7-F_2, 4-Cl, 6-CF **RF_2** = 2-F, 2,6-F_2, 3,4-F_2

D'Angelo et al. [57] conducted the Ullmann type benzthiazole aryl ether **(xxxvii)** synthesis by the reaction of phenol with 2-chlorobenzothiazole involving copper powder and cesium carbonate under microwave condition.



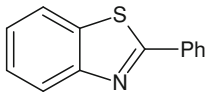
xxxvii

A highly regioselective microwave promoted synthesis of 2-aryl-6-chlorobenzothiazoles **(xxxviii)** by the Suzuki–Miyaura coupling reaction of 2,6-dichlorobenzothiazole with arylboronic acids is given by Heo et al. [58].



xxxviii

Mu et al. [59] reported the microwave assisted synthesis of 2-substituted benzothiazoles **(xxxix)** by the Mn(III)-promoted cyclization of substituted thioformanilides.



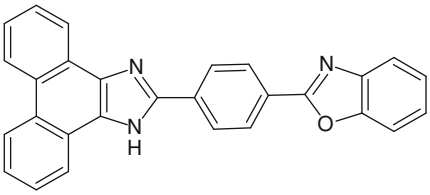
xxxix

10.3 Benzoxazoles

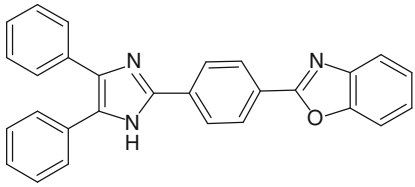
Benzoxazoles are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Substituted benzoxazoles have drawn significant attention due to their biological activity and diverse

medicinal uses such as gram-positive antibacterial agents [60, 61] antibiotics [62] antiparasitic [63] anti-inflammatory [64] elastase inhibitors [65] anti-stress ulcer [66] and anticancer agents [67]. Because of these interesting biological properties, numerous synthetic routes to various benzoxazole derivatives have been reported.

Sun [68] synthesized the 2-(4-(1H-phenanthro [9, 10-d]-imidazol-2-yl)phenyl)-benzoxazole **(xL)** and 2-(4-(4,5-diphenyl-1H–imidazol-2-yl)phenyl)-benzoxazole **(xLi)** nitrogen containing heterocyclic chromophores by using a three-component, one pot reaction under microwave irradiation.

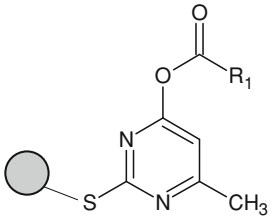


xL

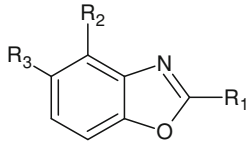


xLi

A collection of highly functionalized benzoxazoles **(xLiii)** have been synthesized by Radi et al. [69] following a one pot, two step microwave assisted, solid-phase synthetic protocol starting from acylating solid supported reagents **(xLii).**



xLii

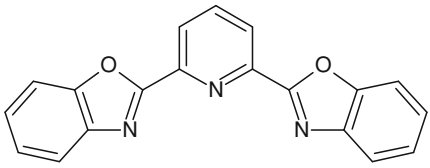


xLiii

R_1 = 4-Chloro-Ph, 2-Fluoro-Ph, 2,4-Difluoro-Ph, 2-Thiophenyl, Acetyl

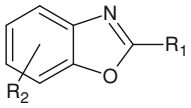
R_2 = H, NO_2 **R_3** = H, Cl, Me

Feng et al. [70] synthesized the 2,6-bis-(benzoxazolyl) pyridine **(xLiv)** by reacting a homogenous mixture of o-aminophenol, 2,6-pyridine carboxylic acid and polyphosphoric acid in a microwave reactor.

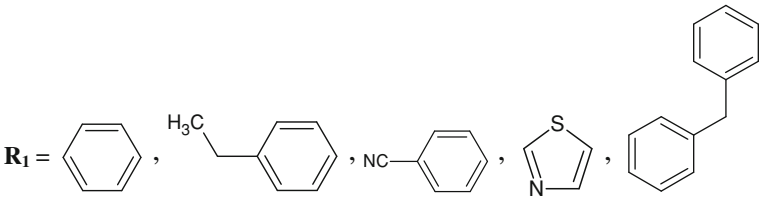


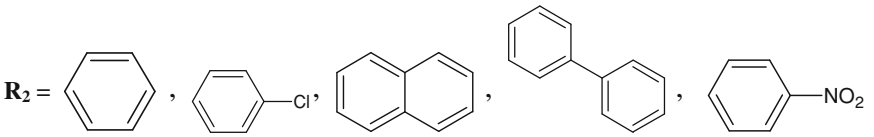
xLiv

Further, the use of commercially available PS-PPh_3 resin combined with microwave condition to lead to a variety of benzoxazoles **(xLv)** in high purities and yields was given by Wang et al. [71]. The protocol involved a one-step reaction of carboxylic acid with 2-amino phenols.

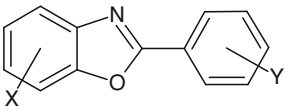


xLv





Pottorf et al. [72] gave the parallel synthesis of a 48-membered library of benzoxazoles **(xLvi)** following a facile route involving the microwave assisted dielectric heating.



xLvi

X = H, Et-SO_2, CH_3, NO_2 **Y** = Br, Ph, NO_2, OMe

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