

REVIEW ARTICLE

GREEN CHEMISTRY APPROACH TO THE SUSTAINABLE ADVANCEMENT TO THE SYNTHESIS OF HETEROCYCLIC CHEMISTRY

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ABSTRACT

In recent decades, a large number of reports related to synthesis of N, O and S containing heterocycles have appeared owing to a wide variety of their biological activity. In recent years, numerous reports concerning the synthesis of heterocycles under solvent-free, reactants immobilized on solid support, microwave irradiation condition have appeared. In this review, we report the important role of solvent-free condition coupled with microwave activation and their advantages in the synthesis of 1,2,4-triazoles, triazines, benzimidazoles and imidazoles, benzoxazoles, 1,3,4-oxadiazoles and 1,2,4-oxazdiazoles, benzothiazoles. Application of microwave irradiation leads to many advantages, like the use of non-corrosive and inexpensive reagents, in addition to the eco-friendly "green chemistry" economical and environmental impacts.

Keywords: Green-chemistry, solvent-free, solid-support, microwave irradiation, heterocycle synthesis.

INTRODUCTION

The first principle of the Rio Declaration on Environment and Development states that “*Human beings are at the centre of concerns for sustainable developments-they are entitled to a healthy and productive life in harmony with nature*”¹, which highlighted the challenge to all of us to define the objectives of *sustainable development* and to provide scientific, technological, and social tools to achieve those objectives

The most important goals of sustainable development are reducing the adverse consequences of the substances that we use and generate. The role of chemistry is essential in ensuring that our next generation of chemicals, materials, and energy is more sustainable than the current generation. Worldwide demand for environmentally friendly chemical processes and products requires the development of novel and cost-effective approaches to pollution prevention. One of the most attractive concepts in chemistry for sustainability is Green Chemistry, which is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products². It should be noted that the rapid development of Green Chemistry is due to the recognition that environmentally friendly products and processes will be economical on a long term.

One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents.

The application of alternative solvents such as water, fluoros and ionic liquids, supercritical media, and their various combinations is rapidly increasing. Catalysis remains one of the most important fields of Green Chemistry by providing atom-economical, selective, and energy efficient solutions to many industrially important problems. The utilization of inorganic^{3,4} solid supported reagents has attracted attention because of enhanced selectivity, milder reaction conditions and associated ease of manipulation. Microwave heating has attracted the attention of investigators in that it makes it possible to shorten the length of reactions significantly, to increase their selectivity, and to increase the product yields, which is particularly important in the case of high-temperature processes that take a long time.

In the last decade microwave radiation (MWR)⁵⁻⁸ has been used more and more often in organic synthesis. In most cases the investigations are carried out in domestic-type microwave ovens or in

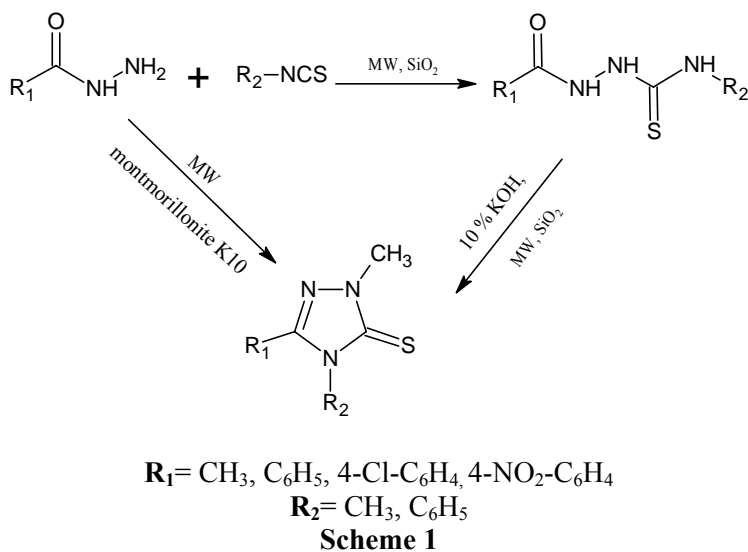
equipment for the preparation of samples and analysis (digests). Microwave equipment specially designed for carrying out organic reactions has also been created⁹⁻¹¹.

Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. Therefore, the goal of the present review is to demonstrate the synthesis of following heterocyclic compounds under green chemistry conventions. The review focuses preferentially on diversity-oriented (multi-component, multi-step one-pot as well as domino) synthesis of:

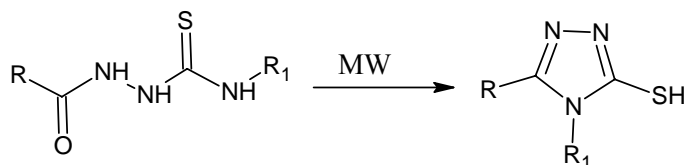
- (1) N, N-containing heterocyclic compounds
 - 1.1.) 1,2,4-Triazoles
 - 1.2.) Triazines
 - 1.3.) Benzimidazoles and Imidazoles
- (2) N, O-containing heterocyclic compounds-
 - 2.1) Benzoxazoles
 - 2.2) 1,3,4-Oxadiazoles and 1,2,4-Oxadiazoles
- (3) N, S-containing heterocyclic compounds-
 - 3.1) Benzothiazoles

1.1 1,2,4-TRIAZOLES

4,5-Disubstituted-1,2,4-triazole-3-thiones have been prepared in one stage from the reaction of acid hydrazide with alkyl or aryl isothiocyanate in the presence of a KOH (10%) solution on the surface of silica gel as well as on the surface of montmorillonite K10 under microwave irradiation. These triazoles have also been prepared from the reaction of 4-substituted-1-aryl thiosemicarbazides, with a KOH (10%) solution on the surface of silica gel under microwave irradiation¹² (**Scheme 1**).



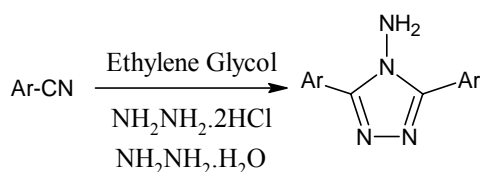
Zamani and Bagheri¹³ have reported different types of 4,5-disubstituted 1,2,4-triazole-3-thiones by microwave irradiation as well as by a classical method. The beneficial effect of microwave irradiation on the dehydrative cyclization of thiosemicarbazides in different reaction media is described. The results show that the effect of microwave irradiation on the reaction studied was the shortening of reaction times (from 2–9 h to 2–4 min) and a minor decrease (1–4%) in yields (**Scheme 2**).



$R_1 =$ (a) 2-pyridyl $R_1 =$ (a) 2-pyridyl 3(a-b), $R' =$ benzyl
 (b) 3-pyridyl (b) 3-pyridyl 4(a-b), $R' =$ 2-methylphenyl
 (c) 4-pyridyl (c) 3-pyridyl
 $R' =$ benzyl $R' =$ 2-methylphenyl

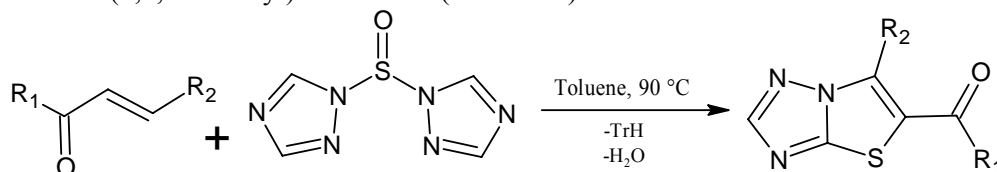
Scheme 2

Bentiss *et al.*¹⁴ have synthesized 3,5-disubstituted-4-amino-1,2,4-triazoles from the reaction of aromatic nitriles with $NH_2NH_2 \cdot 2HCl$ in the presence of $NH_2NH_2 \cdot 2H_2O$ excess in ethylene glycol under microwave irradiation (Scheme 3).



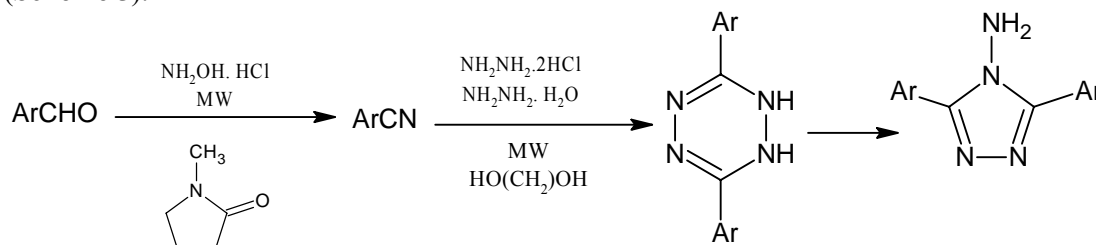
Scheme 3

A novel one-step synthesis of thiazolo-[3,2-*b*]-1,2,4-triazoles were reported from the reaction of chalcones with bis-(1,2,4-triazoly)-sulfoxide¹⁵ (Scheme 4).



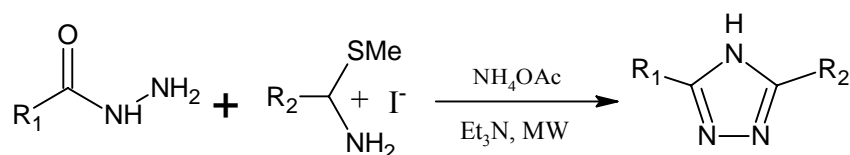
Scheme 4

Symmetrical 3,5-substituted-4-amino-1,2,4-triazoles are quickly prepared from aromatic aldehydes *via* nitriles by two-step reactions without any separation under microwave irradiation for each several minutes¹⁶ (Scheme 5).



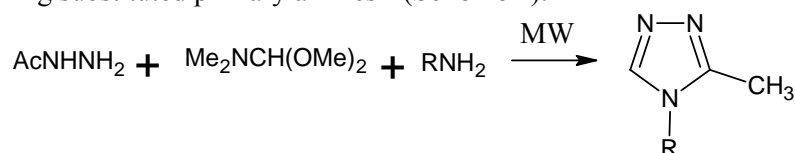
Scheme 5

Condensation of acid hydrazide with *S*-methylisothioamide hydroiodide and ammonium acetate on the surface of silica gel under microwave irradiation afforded 1,2,4-triazoles¹⁷ (Scheme 6).



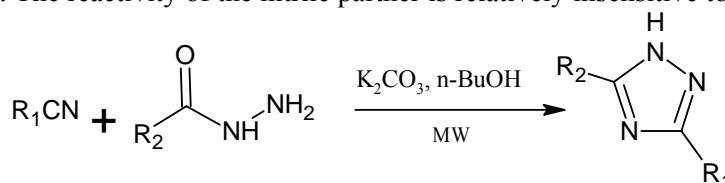
Scheme 6

An efficient microwave-assisted one-pot and three-component synthesis of substituted 1,2,4-triazoles has been achieved utilizing substituted primary amines¹⁸ (Scheme 7).



Scheme 7

A recent publication by Yeung *et al.*¹⁹ described a convenient and efficient one-step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles by the condensation of nitriles and hydrazides under microwave irradiation (Scheme 8). Under the reaction conditions, a diverse range of functionality and heterocycles are tolerated. The reactivity of the nitrile partner is relatively insensitive to electronic effects.



Scheme 8

A new protocol for Biginelli reaction microwave irradiation in the synthesis of some 1,2,4-triazoles as a potential antifungal agents against *Candida albicans* and *Aspergillus niger* has been reported recently²⁰ (fig. 1).

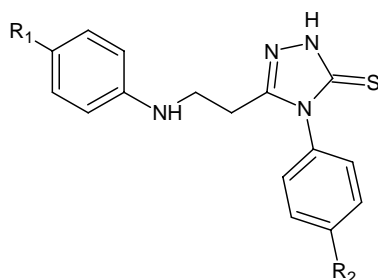
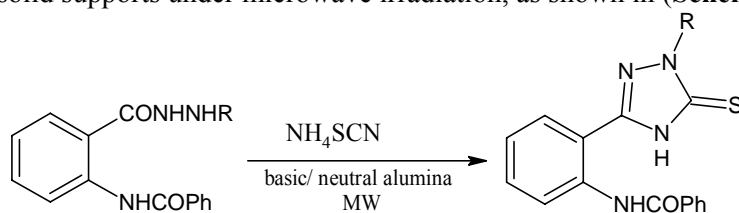


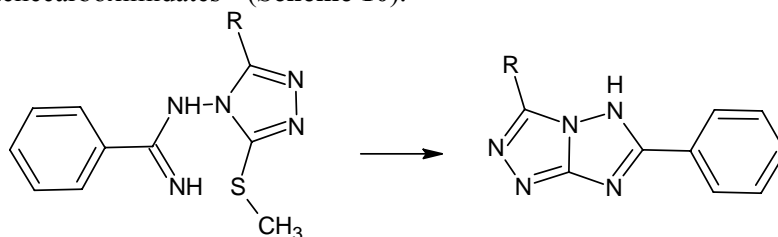
Fig. 1

Kidwai *et al.*²¹ synthesized new antifungal azoles including 1,2,4-triazole derivatives from substituted hydrazide using various solid supports under microwave irradiation, as shown in (Scheme 9).



Scheme 9

A simple and fast synthesis of 6-aryl-3-substituted 5H-[1,2,4]-triazolo-[4,3-*b*][1,2,4]-triazoles in high yields has been developed by microwave assisted heterocyclization of N-(3-methylthio-5-substituted 4H-1,2,4-triazol-4-yl)-benzenecarboximidates²² (**Scheme 10**).

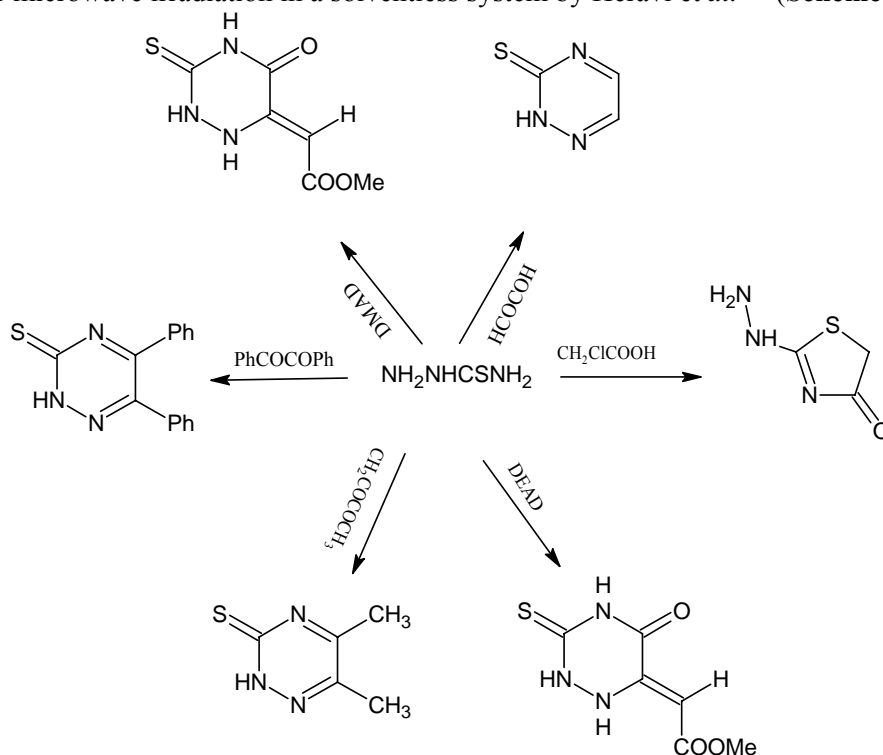


Scheme 10

1.2 TRIAZINES

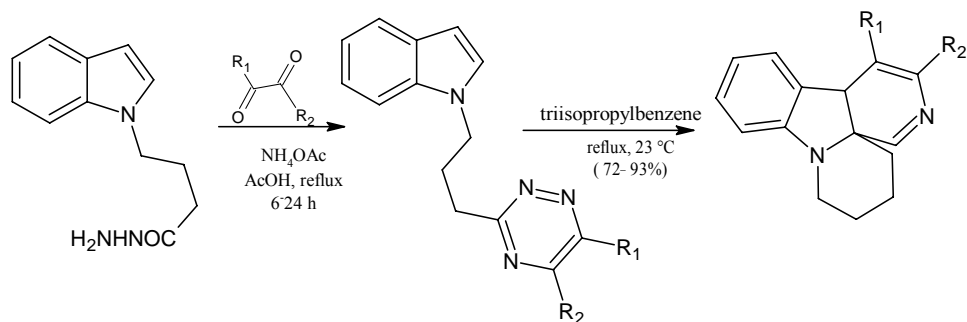
Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology Zhijian Zhao *et al.*²³ developed the rapid synthesis of diverse 3,5,6-trisubstituted 1,2,4-triazines in excellent yield and purity, including many previously unknown 3-heterocyclic-1,2,4-triazines.

1,2,4-triazines were prepared from the condensation of thiosemicarbazide with diketons (RCOCOR, R H, Ph, CH₃) under microwave irradiation in a solventless system by Heravi *et al.*²⁴ (**Scheme 11**).



Scheme 11

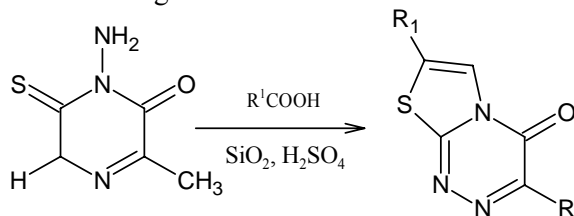
In a one pot microwave reaction, an acyl hydrazide-tethered indole underwent a 3-component condensation to form a triazine, followed by an inverse-electron demand Diels–Alder reaction and subsequent chelotropic expulsion of N₂ to deliver novel, unnatural β-carboline alkaloids in good isolated yields²⁵ (**Scheme 12**).



$R_1=R_2=H, CH_3, COOEt$
 $R_1= C_6H_5, R_2=H,$

Scheme 12

Heravi *et al.*²⁶ reported the synthesis of [1,3,4]-thiadiazolo[2,3-c][1,2,4]-triazin-4-ones were one pot condensation and cyclization of 4-amino-[1,2,4]triazine-3-thione-5-ones with various aromatic carboxylic acids in the presence of silica-gel/sulfuric acid in solventless condition (**Scheme 13**).

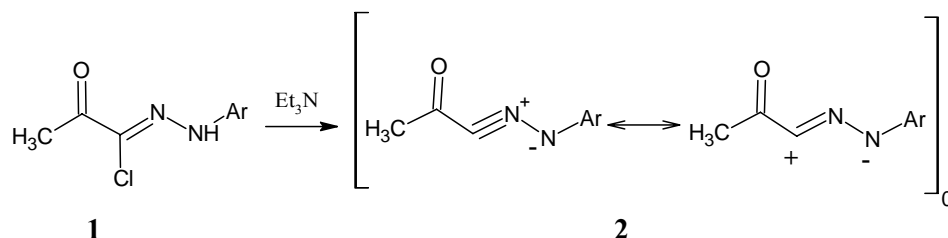


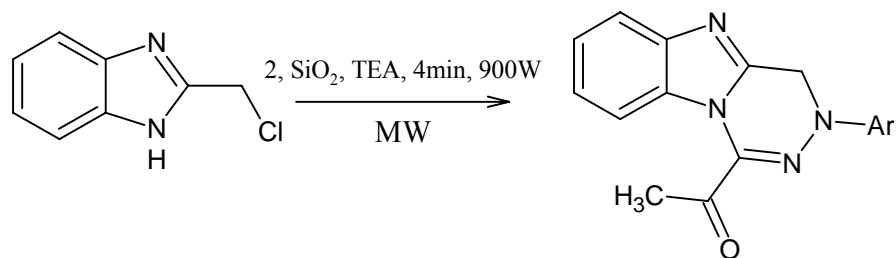
$R_1=C_6H_5, CH_2C_6H_5, 4-CH_3C_6H_5, 3-ClC_6H_5$

Scheme 13

Rostamizadeh and Sadeghi²⁷ have prepared 1,2,4-triazines from the one-pot condensation reaction of acid hydrazide, ammonium acetate and dicarbonyl compounds on the surface of silica gel in the presence of triethylamine under microwave irradiation.

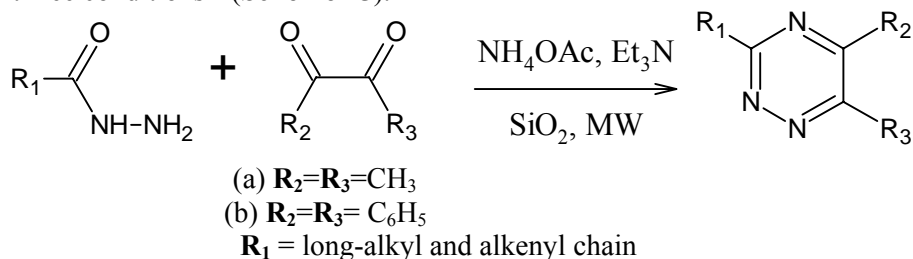
Novel highly functionalized benzimidazoles were synthesized in two steps by microwave irradiation: construction of the benzimidazole ring followed by ring closure to the new tricyclic system. The 1,3-dipole-like nitrile imines were generated in situ from the reaction of triethylamine with the hydrazonyl chlorides. Treatment of with the nitrile imines using microwave irradiation was explored under solvent-free conditions using silica gel as a solid support. The reactants were impregnated on the support and then irradiated at 900 W for 4min using a domestic microwave apparatus (Frigidaire/China) to give the new tricyclic benzimidazole derivatives in 81–88% yields²⁸ (**Scheme 14**).





Scheme 14

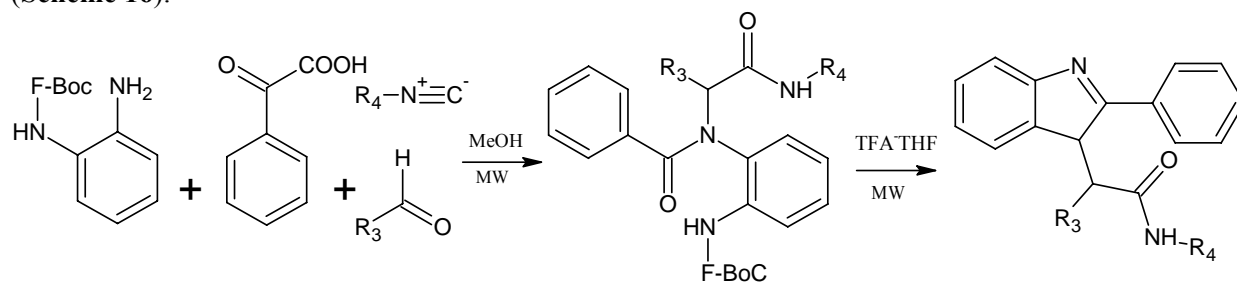
We have synthesized the 3,5,6-trisubstituted-1,2,4-triazines from fatty acid hydrazides under microwave assisted solvent-free conditions²⁹ (Scheme 15).



Scheme 15

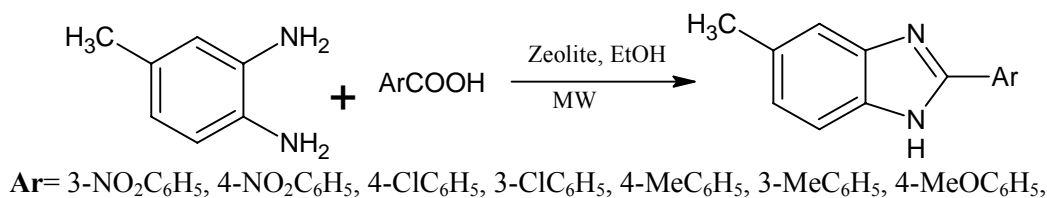
1.3 BENZIMIDAZOLES AND IMIDAZOLES

The efficiency of an Ugi/de-Boc/cyclization strategy for construction of heterocyclic compounds has been improved through the incorporation of microwave and fluorous technologies. In the synthesis of substituted quinoxalinones and benzimidazoles, a fluorous-Boc protected diamine is employed for the Ugi reactions. Both the Ugi and the post-condensation reaction proceed rapidly under microwave irradiation and the reaction mixtures are purified by solid-phase extraction (SPE) over FluoroFlash cartridges³⁰ (Scheme 16).



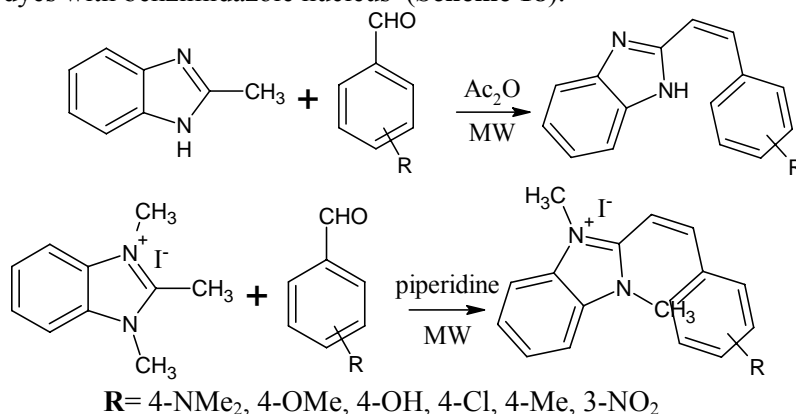
Scheme 16

An efficient and simple synthesis of several 2-arylbenzimidazoles from reaction of 4-methyl-1,2-phenylenediamine and aromatic carboxylic acids in the presence of zeolite catalyst is reported. The reactions were performed under microwave irradiation, and the catalyst could be recycled and used for several times. The yields of products following recrystallization from benzene or dichloromethane were of the order of 26–97%³¹ (Scheme 17).



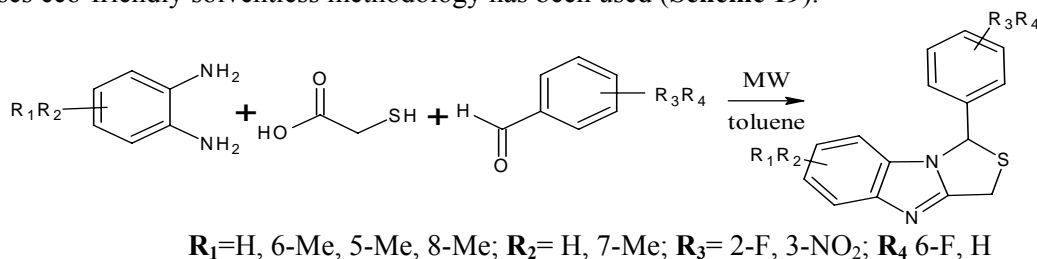
Scheme 17

The reactions of 2-methylbenzimidazole or 2-methylbenzimidazolium iodide with aromatic aldehydes are accelerated under microwave irradiation by using Ac₂O or piperidine as dehydrant or catalyst in the absence of any solvent³². The approach provides an attractive and environmentally friendly pathway to several useful styryl dyes with benzimidazole nucleus (**Scheme 18**).



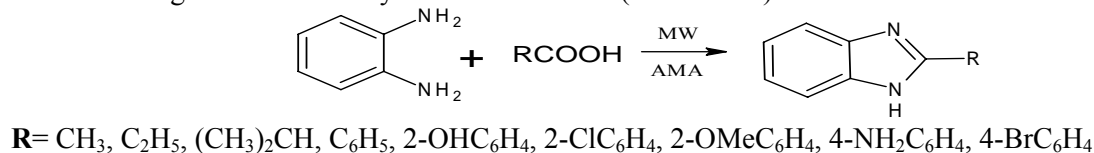
Scheme 18

Rao *et al.*³³ has described the microwave-assisted synthesis of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles, 2-aryl-1-benzylbenzimidazoles and 2,3-diaryl-1,3-thiazolidin-4-ones, which achieved reductions in reduced reaction times, higher yields, cleaner reactions than for the previously described synthetic processes. In some cases eco-friendly solventless methodology has been used (**Scheme 19**).



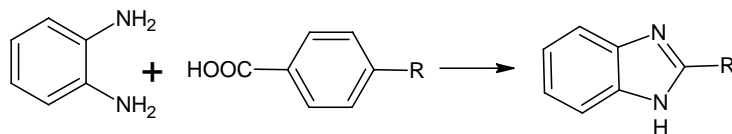
Scheme 19

A microwave-assisted method for the synthesis of 2-substituted benzimidazoles in the presence of alumina-methanesulfonic acid (AMA) is reported³⁴. In addition, by this method some new bis-benzimidazoles from the direct reaction of phenylenediamine and dicarboxylic acid under microwave irradiation in good to excellent yields are described (**Scheme 20**).



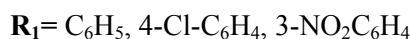
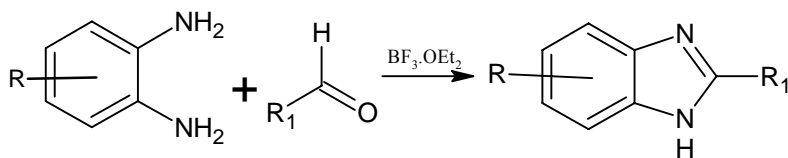
Scheme 20

The synthesis of 2-substituted benzimidazole, benzothiazole and indole derivatives using both microwave irradiation and conventional heating methods was reported³⁵. The microwave method was observed to be more beneficial as it provides an increase of yield from 3% to 113% and a 95 to 98 % reduction in time. All compounds were tested by a stains-all assay at pH 7 and by a Morgan-Elson assay at pH 3.5 for hyaluronidase inhibitory activity at a concentration of 100 μ M. The most potent compound was 2-(4- hydroxyphenyl)-3-phenylindole with an IC₅₀ value of 107 μ M at both pH 7 and 3.5 (**Scheme 21**).

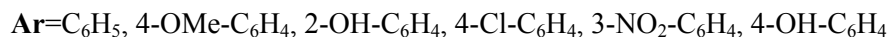
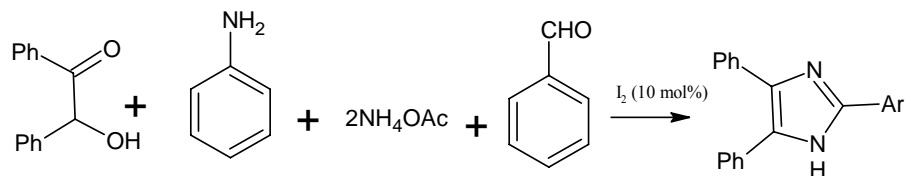
**Scheme 21**

Transition metal/Y zeolites were prepared using microwave solid state and aqueous solution ion exchange methods. The activity of these zeolites was investigated in a conversion of acids to benzimidazoles reaction between 4-methyl-1, 2-phenylenediamine and 3-nitrobenzoic acid. The yield of these reactions increased in order of CuY < Fe²⁺Y < NiY < CoY < NaY < CrY < MnY < ZnY for both methods. The solid state ion-exchanged zeolites showed higher activity in comparison to the aqueous solution exchange. Yields of products in the presence of the ZnY zeolite were of the order of 69–83%. It seems that the Lewis sites are better sites compared to the Bronsted sites for this reaction³⁶.

Differently substituted benzimidazoles have been synthesized in very good yields in solvent-free conditions from *o*-phenylenediamine and aldehydes in the presence of BF₃·OEt₂ as a catalyst³⁷. The method is applicable to aromatic, unsaturated and aliphatic aldehydes and to substituted *o*-phenylenediamines without significant differences (**Scheme 22**).

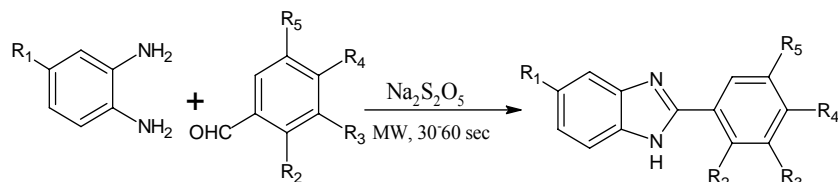
**Scheme 22**

Molecular iodine is a cheap, nontoxic catalyst, which acts as an efficient catalyst for the synthesis of 1,2,4,5-tetraarylimidazoles using benzoin, an aromatic aldehyde and an amine in the presence of ammonium acetate³⁸. The advantage of this method is the direct use of benzoin, which is transformed into benzil in situ and condenses further to generate the imidazole in a one-pot sequence (**Scheme 23**).

**Scheme 23**

A series of 2-(substituted phenyl)-1*H*-benzimidazole derivatives with various 5- and 6-position substituents (-H, -CH₃, -CF₃) were synthesized via microwave irradiation using a short synthetic route and

$\text{Na}_2\text{S}_2\text{O}_5$ as oxidant³⁹. This simple, fast, and efficient preparation of benzimidazole derivatives has been developed using readily available and inexpensive reagents (aldehydes and 1,2-phenylenediamines) under solvent-free conditions (**Scheme 24**).



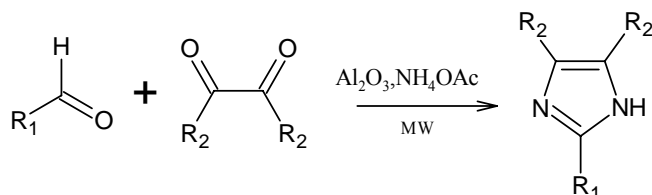
$\text{R}_1 = \text{H}, \text{CH}_3, \text{CF}_3,$

$\text{R}_2 = \text{H}, \text{OCH}_3, \text{NO}_2, \text{OCH}_2\text{CH}_3; \text{R}_3 = \text{H}, \text{OCH}_3; \text{R}_4 = \text{H}, \text{OH}, \text{OCH}_3, \text{N}(\text{CH}_3)_2; \text{R}_5 = \text{H}, \text{OCH}_3$

Scheme 24

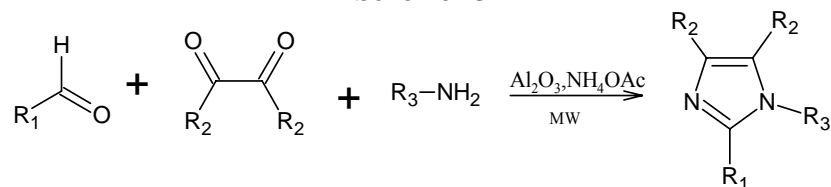
A new and efficient method for the preparation of 2-amino-imidazole **3** was developed. Starting from cheap commodities *O*-methyl-iso-urea sulphate and 2-aminoacetaldehyde-acetales the desired product is isolated through a very simple work-up in a good yield. This new procedure overcomes several technical and environmental problems of the traditional approaches to this molecule and is therefore very attractive for large-scale preparation⁴⁰.

The solvent-free microwave-assisted synthesis of 2,4,5-substituted and 1,2,4,5-substituted imidazoles is reported. Imidazoles are obtained as a result of the condensation of a 1,2-dicarbonyl compound with an aldehyde and an amine using acidic alumina impregnated with ammonium acetate as the solid support⁴¹ (**Scheme 25, 26**).



$\text{R}_1 = \text{R}_2 = \text{C}_6\text{H}_5$

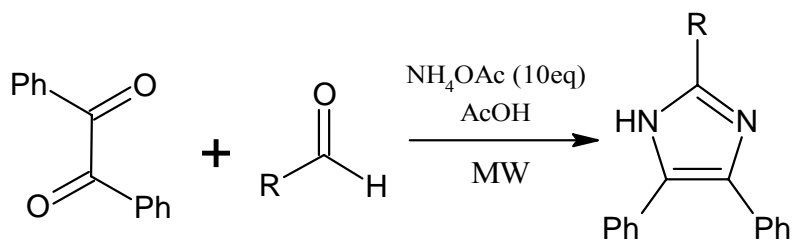
Scheme 25



$\text{R}_1 = \text{R}_2 = \text{C}_6\text{H}_5 \quad \text{R}_3 = \text{CH}_3$

Scheme 26

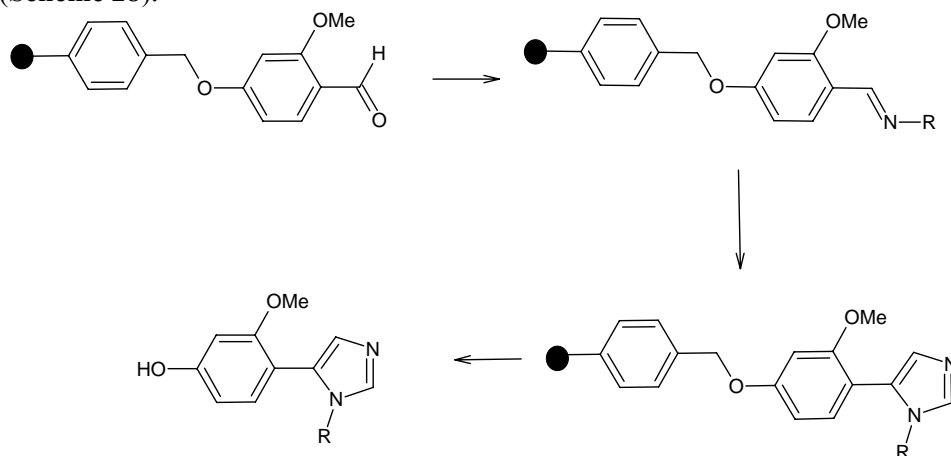
A simple, high-yielding synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketones and aldehydes in the presence of NH_4OAc is described. Under microwave irradiation, alkyl-, aryl-, and heteroaryl-substituted imidazoles are formed in yields ranging from 80 to 99%. Short syntheses of lepidiline B and trifenagrel illustrate the utility of this approach⁴² (**Scheme 27**).



R= 4-F-C₆H₄, 4-CN-C₆H₄, 4-OMe-C₆H₄

Scheme 27

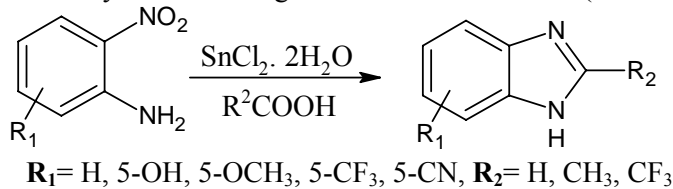
A convenient method for the synthesis of 1,5-disubstituted imidazoles has been developed on a polymeric support using base-promoted 1,3-dipolar cycloaddition reaction of p-toluenesulfonylmethyl isocyanide (TOSMIC) with immobilized imines under microwave irradiation⁴³. The immobilized imines were synthesized by the reaction of various primary benzyl amines with 4-formyl-3-methoxyphenoxyethyl polystyrene in the presence of trimethyl orthoformate at room temperature. Cleavage from the polymeric support using trifluoroacetic acid gave the desired 1,5-disubstituted imidazoles with excellent yield and high purity (**Scheme 28**).



R= 3-ClC₆H₄CH₂, 4-ClC₆H₄CH₂, 2-OMeC₆H₄CH₂, 4-ClC₆H₄CH₂

Scheme 28

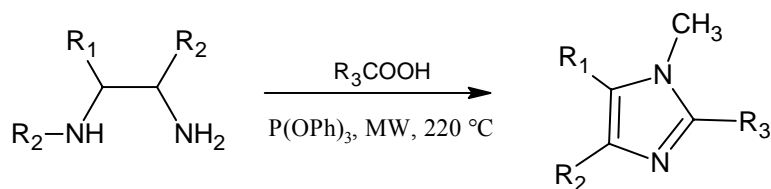
VanVliet *et al.* have reported the the generation of 2-substituted-benzimidazoles directly from 2-nitroanilines by insitu reduction and cyclization using microwave irradiation⁴⁴ (**Scheme 29**).



R₁= H, 5-OH, 5-OCH₃, 5-CF₃, 5-CN, R₂= H, CH₃, CF₃

Scheme 29

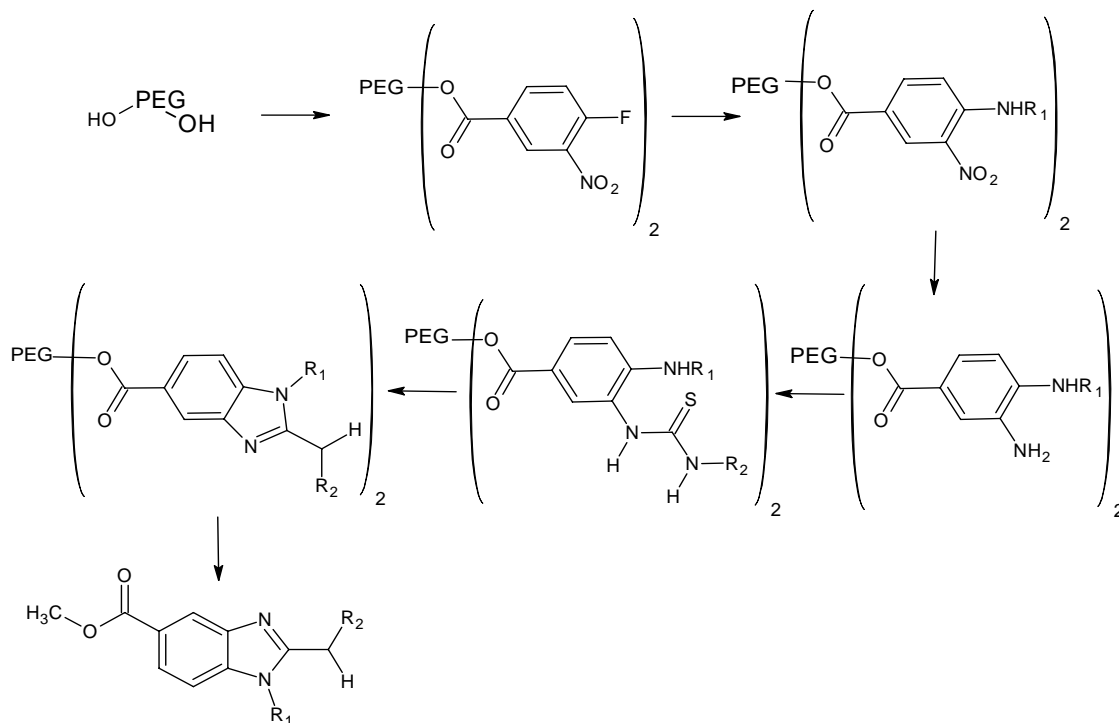
One-pot synthesis of benzimidazoles from diamines and carboxylic acids was developed under microwave irradiation condition, which provided a practical and efficient method for high-throughput synthesis of this important class of heterocyclic compounds⁴⁵ (**Scheme 30**).

**Scheme 30**

An efficient, microwave-assisted method for the mercury chloride mediated synthesis of 1,2-disubstituted benzimidazoles has been developed. Biologically interesting benzimidazoles were readily assembled utilizing S_NAr reactions, reduction, and followed with mercury (II) mediated cyclization under microwave irradiation. The desired products were then liberated from the soluble matrix in excellent yield and purity after cleavage⁴⁶.

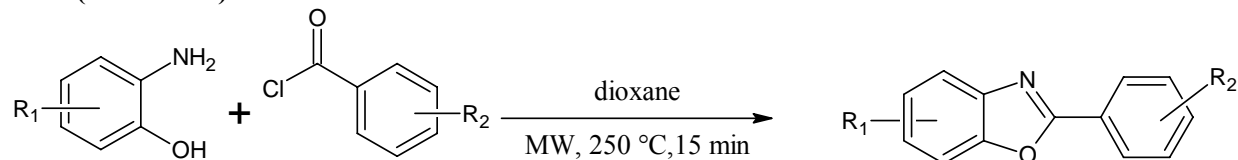
Liquid phase combinatorial synthesis using a soluble polyethylene glycol (PEG) polymer support and commercially available 3-nitro-4-fluoro benzoic acid is carried out in order to create a molecular library of trisubstituted benzimidazoles. The PEG-ester conjugate of 3-nitro-4-fluoro benzoic acid is subjected to ipso-fluoro displacement by various primary amines. The nitro group is reduced under neutral conditions using excess zinc and ammonium chloride, producing the polymer-bound O-phenylene diamines. Reaction of the diamines with different aldehydes results in cyclisation to benzimidazoles. The polymer support is cleaved releasing the desired products in high yields and purity. All reactions are performed at room temperature⁴⁷.

A multistep liquid phase synthesis of specifically functionalized bis-benzimidazoles is presented by the application of single-mode microwave irradiation technique. The sustained solubilizing power and stability of the PEG-ester derived from the commercially available 4-fluoro-3-nitrobenzoic acid has been successfully carried through 10 steps involving ipso- S_NAr reaction, neutral reduction and acid cyclization. All the steps in this synthetic sequence were assisted by microwave (MW) irradiation. The polymer support was cleaved to release the final head to tail bisbenzimidazoles in an efficient process⁴⁸ (**Scheme 31**).

**Scheme 31**

2.1 BENZOXAZOLES

Benzoxazoles under MW are routinely prepared in a two-step sequence comprising base-catalyzed bisacylation of *ortho*-aminophenols followed by a Lewis-acid-assisted cyclization-dehydration reaction. Microwave flash heating of readily available acid chlorides and *ortho*-aminophenols in sealed reaction vessels delivered benzoxazoles in a one-pot process without aid of any additive such as base or Lewis acid⁴⁹ (Scheme 32).

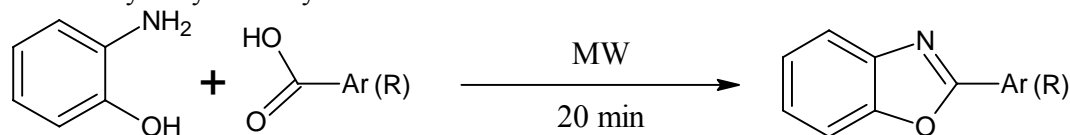


R¹ = H, EtS-, EtCH(CH₃)₂, CH₃, NO₂, 2-NO₂, 2-naphthyl

R² = Br, C₆H₅, 4-Br, 4-NO₂, 3,4,5-OMe

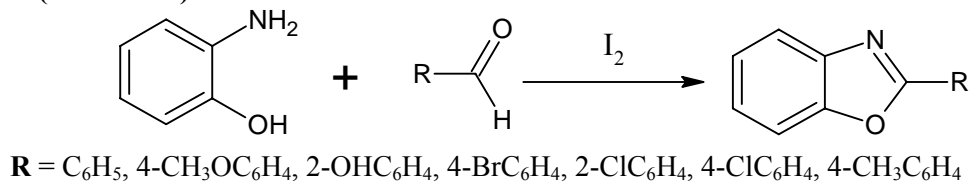
Scheme 32

In a closed related publication, carboxylic acids were employed instead of acid chloride in a microwave-assisted direct synthesis of 2-substituted benzoxazoles⁵⁰ (Scheme 33). The reactions with 2-aminophenol were performed in a household microwave oven and worked well with aromatic, heteroaromatic, α,β -unsaturated and aryl alkyl carboxylic acids.



Scheme 33

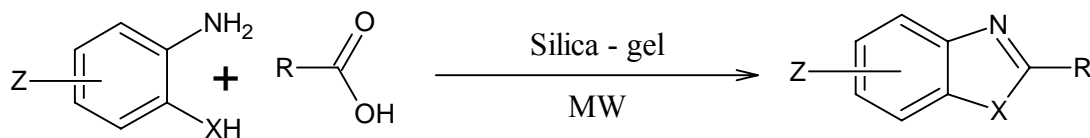
Recently, 2-substituted benzoxazoles by condensation of 2-aminophenol with various aromatic aldehydes using molecular iodine as catalyst under solvent free conditions with or without microwave irradiation is reported⁵¹ (Scheme 34).



R = C₆H₅, 4-CH₃OC₆H₄, 2-OHC₆H₄, 4-BrC₆H₄, 2-ClC₆H₄, 4-ClC₆H₄, 4-CH₃C₆H₄

Scheme 34

Martinez-Palou and co-workers⁵² have generated a 40-membered library of compounds from readily available aromatic 2-substituted amines and fatty acids by means of two efficient microwave-assisted protocols. A parallel synthesis using a monomode microwave (MOMW), and an automated procedure using a multimode microwave (MUMW) and a robotic liquid handler were also described (Scheme 35).

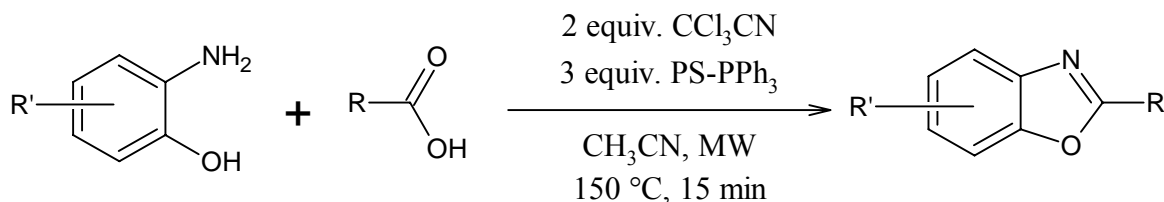


X = O, NH, Z = H, Me, Cl, R = Long-alkyl chain

Scheme 35

Wang *et al.*⁵³ synthesized benzoxazoles from carboxylic acids and 1,2-aminophenol with PS-PPh₃/CCl₃CN (Scheme 36).

PS-

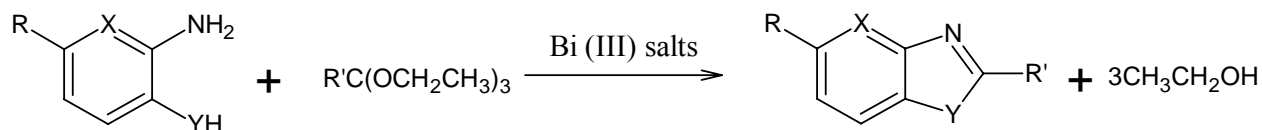


$R = C_6H_5, C_6H_4CH_2CH_2, C_6H_4N(CH_3)_2, C_6H_4CN, 1,3$ thiazole

$R' = CH_3, NO_2, C_6H_5, Cl, CH_3COO$

Scheme 36

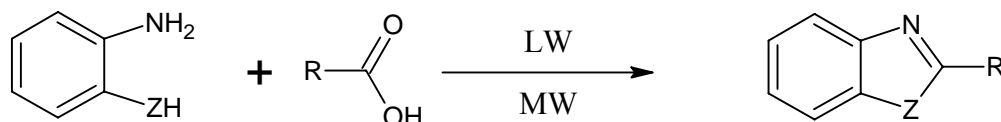
Baltork *et al.*⁵⁴ developed a very simple and convenient protocol for the synthesis of 2-substituted benzoxazoles, benzothiazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines using catalytic amounts of Bi (III) salts under solvent-free conditions (**Scheme 37**).



$R = CH_3, H, Cl, R' = CH_3CH_2, CH_3, H, X = C, N, Y = O, NH, S$

Scheme 37

Seijas and co-workers⁵⁵ have developed Lawesson's reagent (LW) and microwaves for the efficient access to benzoxazoles and benzothiazoles from carboxylic acids under solvent-free conditions (**Scheme 38**).

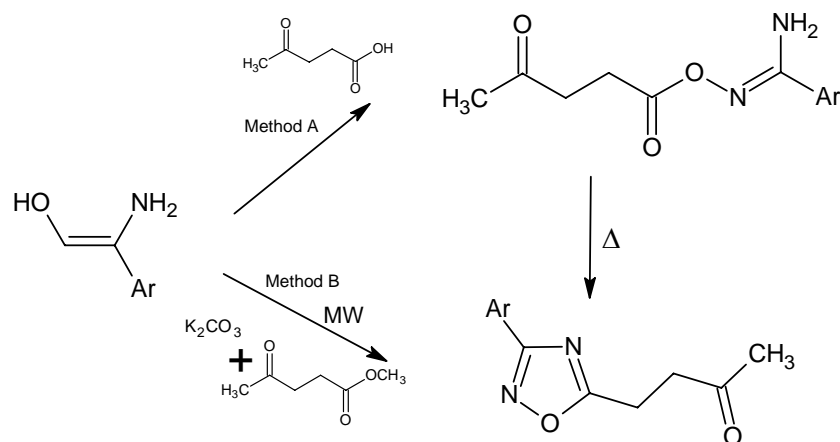


$Z = O, N, R = C_6H_5, 3,4-(MeO)_2C_6H_3, 2,3-(MeO)_2C_6H_3, 2-MeOC_6H_4, 2,4,5-(OMe)_3C_6H_2, 3-MeC_6H_4, 4-ClC_6H_4, 1$ -naphthyl, 2-naphthyl, 2-pyridinyl, 2-thienyl, 2-phenylethenyl, Bn, 3,4-(MeO)₂C₆H₃CH₂, C₆H₁₃, C₁₁H₂₃, C₁₇H₃₅

Scheme 38

2.2 1,3,4-OXADIAZOLES AND 1,2,4-OXADIAZOLES

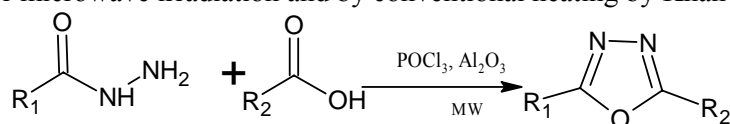
de Freitas *et al.*⁵⁶ synthesized the 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-ones from methyl levulinate and arylamidoximes. The reaction was carried out in a microwave oven without any solvent in much shorter time and in yields comparable with conventional heating. (**Scheme 39**).



Ar = C₆H₅, 2-CH₃C₆H₄, 3-CH₃C₆H₄, 4-ClC₆H₄, 3-BrC₆H₄, 4-BrC₆H₄, 3-NO₂C₆H₄, 4-NO₂C₆H₄, 2-CH₃O C₆H₄, 3-CH₃O C₆H₄, 4-CH₃OC₆H₄

Scheme 39

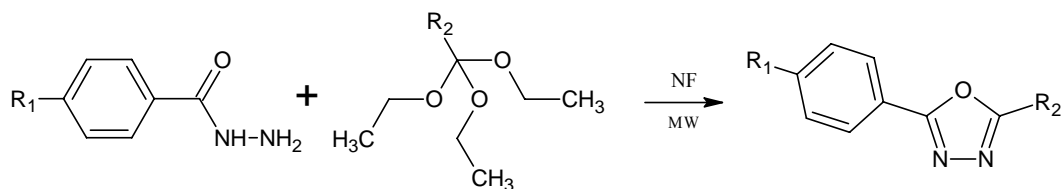
2,5-Disubstituted-1,3,4-oxadiazoles were synthesized from pyridinyl hydrazide and various substituted carboxylic acids under microwave irradiation and by conventional heating by Khan *et al.*⁵⁷ (**Scheme 40**).



R₁ = 3-pyridinyl; **R**₂ = C₆H₅, 2-NO₂C₆H₄, 2-BrC₆H₄, 3-BrC₆H₄, 4-BrC₆H₄, 3-pyridinyl, CH₂Cl, CHCl₂, CCl₃, 4-CH₃C₆H₄, 3,4,5-Trimethoxy benzoyl, 1-C₁₀H₇, 2-C₁₀H₇

Scheme 40

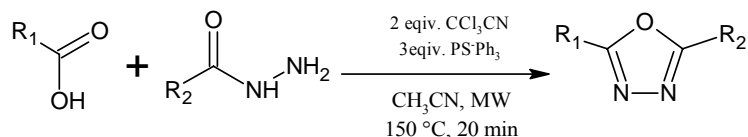
A novel one-pot solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles by condensation of acid hydrazide and triethyl orthoalkanoates under microwave irradiations was reported by Polshettiwar and Varma⁵⁸. This green protocol was catalyzed efficiently by solid supported Nafion[®] NR50 (NF) and phosphorus pentasulfide in alumina (P₄S₁₀/Al₂O₃) with excellent yields (**Scheme 41**).



R₁ = H, F, OMe, 2-furyl, 2-thienyl, 4-pyridyl; **R**₂ = H, Et, C₆H₅

Scheme 41

1,3,4-Oxadiazoles can be rapidly and efficiently synthesized from a variety of carboxylic acids and acid hydrazides in one simple step⁵⁹. The use of commercially available PS-PPh₃ resin combined with microwave heating delivered the product 1,3,4-oxadiazoles in high yields and purities (**Scheme 42**).

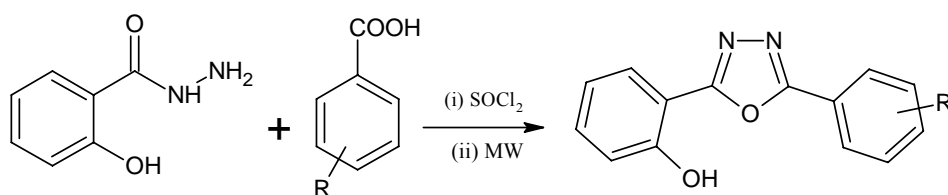


$R_1 = C_6H_5, -C_6H_5, C_6H_5, C_6H_{11}$; $R_2 = C_6H_5, 3-FC_6H_4, 3-OMeC_6H_4, 3-NO_2C_6H_4$

Scheme 42

*Evans et al.*⁶⁰ report the development of an optimized microwave-assisted synthesis of 1,2,4-oxadiazoles. The chemistry development process was significantly accelerated by employing a statistical software package (MODDE 6.0™) to guide in the optimization of the reaction conditions. The resulting optimized reaction conditions were then utilized in the synthesis of a focused library of 1,2,4-oxadiazoles.

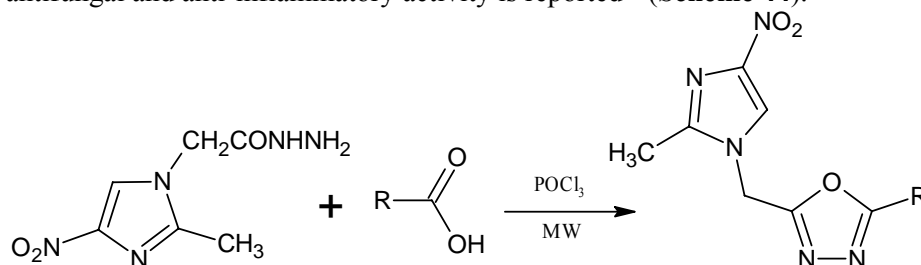
An efficient, rapid, microwave-accelerated one-step synthesis of some 5-aryl-2-(2-hydroxy-phenyl)-1,3,4-oxadiazoles by reaction of salicylic hydrazide with carboxylic acids in the presence of thionyl chloride under neat conditions is described⁶¹ (Scheme 43).



$R = H, 4-Me, 4-MeO, 3,4-(MeO)_2, 3,4,5-(MeO)_3, 3-Cl, 2-Br, RC_6H_4 = 3-MeOC_6H_4CH_2$

Scheme 43

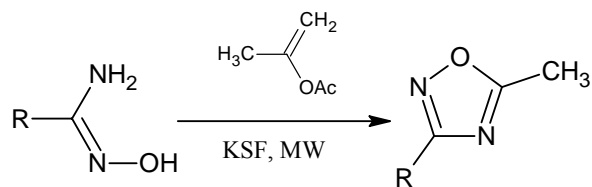
Microwave-assisted as well as conventional synthesis of 5-substituted-2-(2-methyl-4-nitro-1-imidazolmethyl)-1,3,4-oxadiazoles containing the nitroimidazole moiety is carried out and their antibacterial, antifungal and anti-inflammatory activity is reported⁶² (Scheme 44).



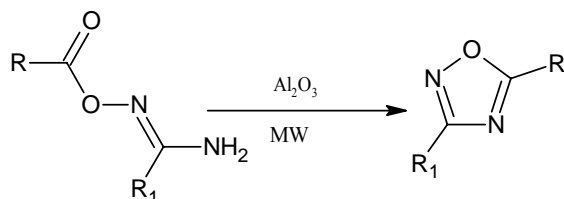
$R = C_6H_5, 4-CH_3C_6H_4, 4-OCH_3C_6H_4, 4-ClC_6H_4, 2-CH_3C_6H_4, C_5H_4N, 2-C_4H_3O, C_6H_5-OCH_2, 4-CH_3-C_6H_4-OCH_2, 2-CH_3-C_6H_4-OCH_2, 4-Cl-C_6H_4-OCH_2, 4-Cl-2-CH_3-C_6H_3-OCH_2$

Scheme 44

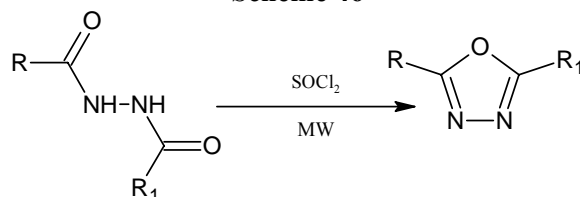
Amidoximes reacted with isopropenyl acetate in presence of KSF under microwave irradiation and gave 1,2,4-oxadiazoles. 1,2,4-Oxadiazoles can also be obtained by microwave irradiation from O-acylamidoximes adsorbed on alumina. 1,3,4-Oxadiazoles were obtained by irradiation of bis (acyl) hydrazines in thionyl chloride⁶³ (Scheme 45-47).



Scheme 45

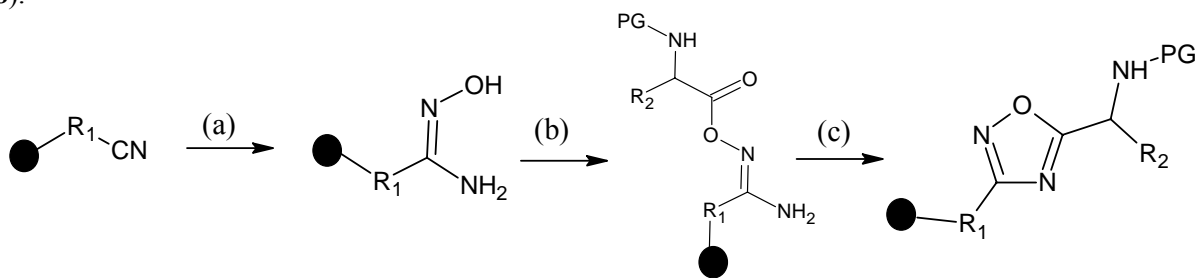


Scheme 46



Scheme 47

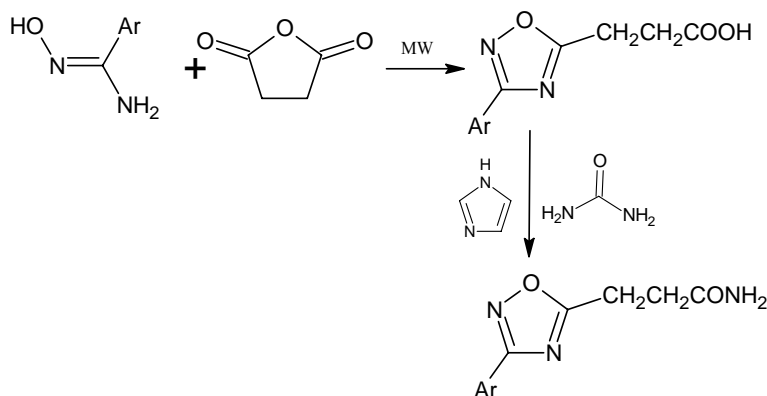
Aliphatic and aromatic nitriles linked to solid support were converted to amide oximes, and cyclized to oxadiazoles using N-protected amino acid anhydrides. The amino protecting group was removed and the products acylated or sulfonylated on resin to provide combinatorial libraries of oxadiazoles⁶⁴ (**Scheme 48**).



- (a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, DIEA, $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$, 85°C , 16 h; (b) Boc-AA- CO_2H or Fmoc-AA- CO_2H , DIC, 2-methoxyethyl ether, rt, 1 h, then 60°C , 16 h; (c) 2-methoxyethyl ether, 85°C , 6 h

Scheme 48

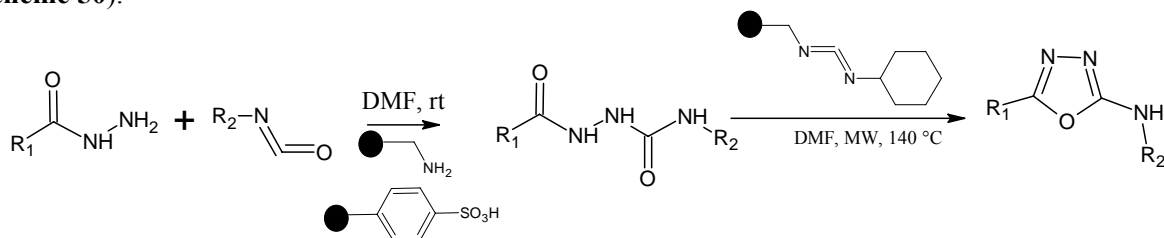
A one-step, simple and straightforward synthesis of the title amides from the corresponding carboxylic acids, urea and imidazole under microwave irradiation is described⁶⁵ (**Scheme 49**).



Ar = C₆H₅, 2-CH₃ C₆H₅, 3-CH₃ C₆H₅, 4-CH₃ C₆H₅, 4-CH₃O C₆H₅, 4-Br C₆H₅

Scheme 49

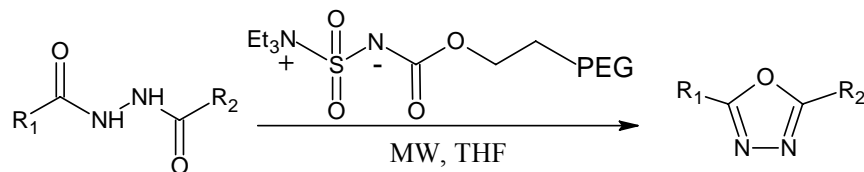
The library of 5-substituted-2-amino-1,3,4-oxadiazoles and the corresponding thiadiazole analogues by Baxendale *et al.*⁶⁶. The one-pot preparation of the 2-aminosulfonylated analogues through a three component coupling of an acylhydrazine, an isocyanate and sulfonyl chloride promoted by a polymer-supported phosphazine base was carried out under microwave dielectric heating. The optimization process and details pertaining to the elucidation of the reaction products were also described in paper (Scheme 50).



R₁ = C₆H₅, 4-OMe-C₆H₄, 2-NO₂-C₆H₄, 2-Cl-C₆H₄, CH₃CO-, C₄H₃O-
 R₂ = 4-NO₂C₆H₄, 2-Cl-C₆H₄, 2-CF₃-C₆H₄, 4-COOMe-C₆H₄, 3-NO₂-4-F-C₆H₃

Scheme 50

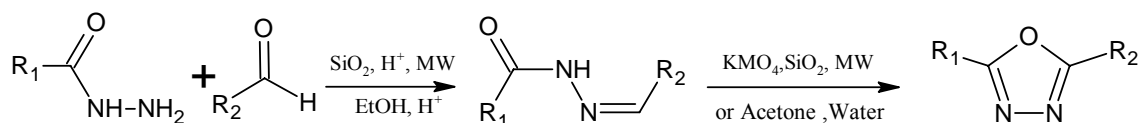
A novel and efficient means of effecting the cyclodehydration of 1,2-diacylhydrazines to provide 1,3,4-oxadiazoles is reported⁶⁷. Polymer supported Burgess reagent was utilised in combination with singlemode microwave heating (Scheme 51).



R₁ = Ph, 2-MeO-C₆H₅, 3-MeO-C₆H₅, 4-MeO-C₆H₅, 2-Cl-C₆H₅, 2-NO₂C₆H₅, 2-Thiophenyl, 2-Furyl, 3-Pyridyl, 4-Pyridyl, C₆H₅SO₂CH₂
 R₂ = C₆H₅, Me, NHC₆H₅

Scheme 51

2,5-Disubstituted-1,3,4-oxadiazoles have been synthesized by oxidation of 1-aroil-2-arylidene hydrazines with potassium permanganate on the surface of a solid mineral support as well as in mixtures of acetone and water under microwave irradiation⁶⁸ (Scheme 52).

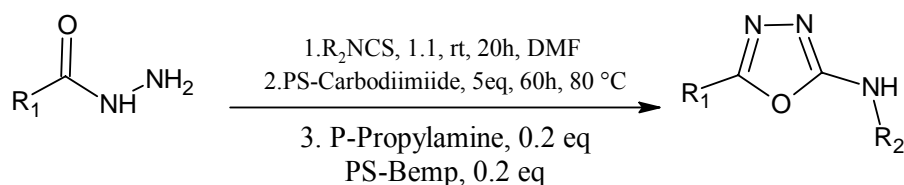


$R_1 = C_6H_5, 4-Cl-C_6H_4$

$R_2 = C_6H_5, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-CN-C_6H_4, 4-MeOOC-C_6H_4, 4-(Me)_2N-C_6H_4, Me, CH_3CH=CH-$

Scheme 52

A robust efficient one-pot preparation of 5-substituted-2-amino-1,3,4-oxadiazoles using resin-bound reagents directly from acylhydrazines and isothiocyanates is described⁶⁹. Commercially-available polymer-supported reagents help to facilitate both cyclization and purification. This convenient method benefits from its broad applicability, ease and safety of reagent handling, simple product isolation, and the ability to perform multiple reactions in parallel fashion without need for purification (Scheme 53).

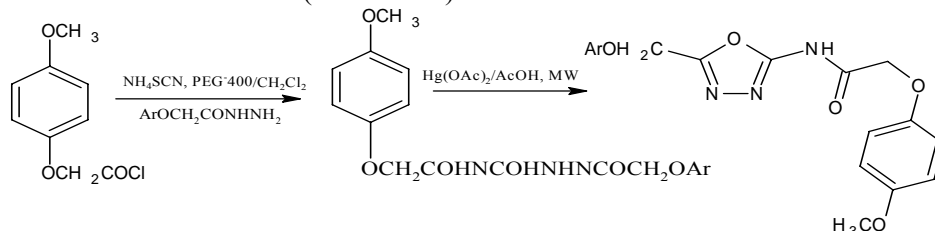


$R_1 = C_6H_5, 2-F-6-Cl-C_6H_5CH_2, 3,4-Di-Cl-C_6H_5CH_2, 3-Pyridyl-CH_2, 3,4-OCH_2OC_6H_5CH_2, 2-F-6-Cl-C_6H_5CH_2, 3,4-Di-Cl-C_6H_5CH_2, 3-Pyridyl-CH_2, 3,4-OCH_2OC_6H_5CH_2$

$R_2 = C_6H_5, isobutyl, CH_3$

Scheme 53

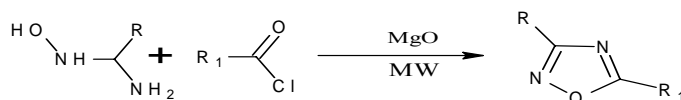
2-(4-Methoxyphenoxyacetyl-amido)-5-aryloxymethyl-1,3,4-oxadiazoles are synthesized by cyclization of 1-aryloxyacetyl-4-(4-methoxyphenoxyacetyl)-thiosemicarbazides in the presence of mercuric acetate under microwave irradiation⁷⁰ (Scheme 54).



$Ar = C_6H_5, 2-CH_3C_6H_4, 3-CH_3OC_6H_4, 4-ClC_6H_4, 1-Naphthyl, 2-NO_2C_6H_4, 3-NO_2C_6H_4, 4-NO_2C_6H_4$

Scheme 54

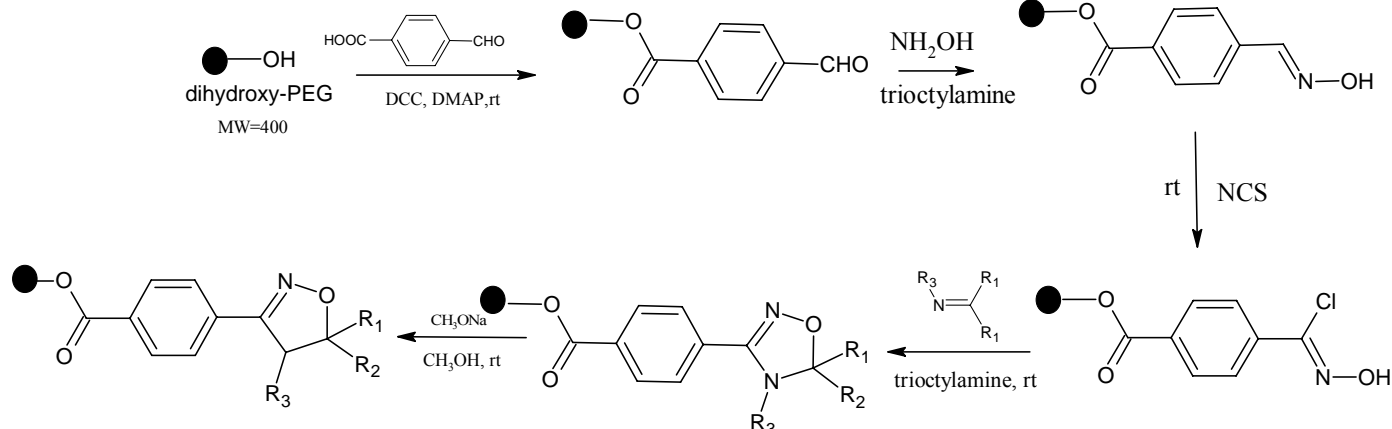
Microwave-assisted synthesis of 1,2,4-oxadiazoles of amidoximes under solvent free conditions was found to be an efficient method for one-pot synthesis of 1,2,4-oxadiazole derivatives from amidoximes and acyl chlorides. The method given by Kaboudin and Navaee⁷¹ is an easy, rapid, and high-yielding reaction for the synthesis of 1,2,4-oxadiazoles (Scheme 55).



$R = C_6H_5, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-Cl_2C_6H_3, 4-ClC_6H_4CH_2, C_6H_5-CH=CH, C_6H_{11}, 4-ClC_6H_4CH_2, 3-ClC_6H_4$

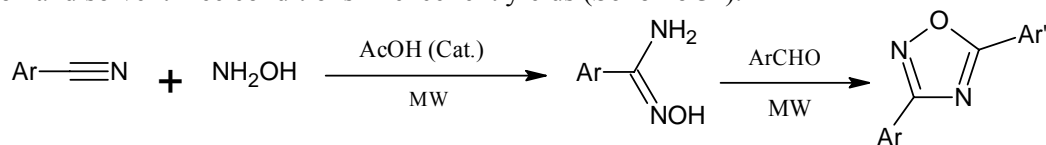
Scheme 55

1,3-Dipolar cycloadditions of nitrile oxide generated in situ on soluble polymer with a variety of imines provided a library of 4,5-dihydro-1,2,4-oxadiazoles in good yields and purity⁷² (Scheme 56).



Scheme 56

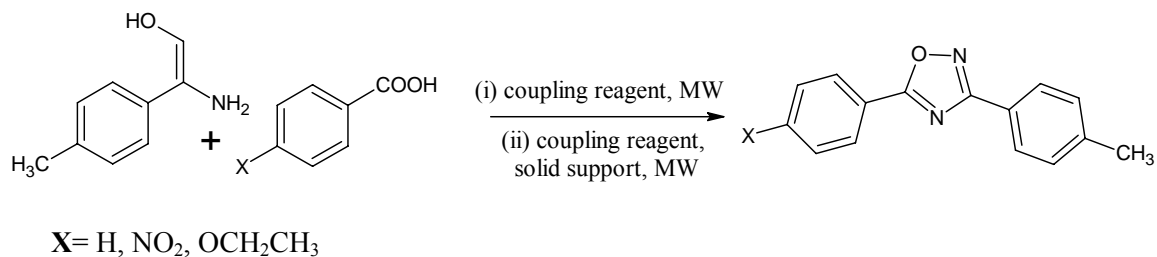
Adib *et al.*⁷³ reported the one-pot, three component condensation reaction between nitriles, hydroxylamine and aldehydes for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles under microwave irradiation and solvent-free conditions in excellent yields (Scheme 57).



Ar = C₆H₅, 4-CH₃C₆H₄, 3-ClC₆H₄, Ar' = C₆H₅, 4-CH₃C₆H₄, 4-ClC₆H₄, 4-CH₃OC₆H₄

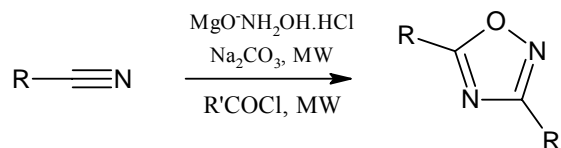
Scheme 57

Santagada *et al.*⁷⁴ have reported the one-pot microwave assisted synthesis of substituted-1,2,4-oxadiazoles in solvent and under solvent-free condition was performed exploring the importance of some coupling reagents. Good yields and shorter reaction times were the main aspects of the methods (Scheme 58).



Scheme 58

Kaboudin and Saadati⁷⁵ has developed the efficient method for the synthesis of 1,2,4-oxadiazoles through one-pot reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia supported sodium carbonate followed by reaction with acyl halides under solvent-free conditions using microwave irradiation (Scheme 59).



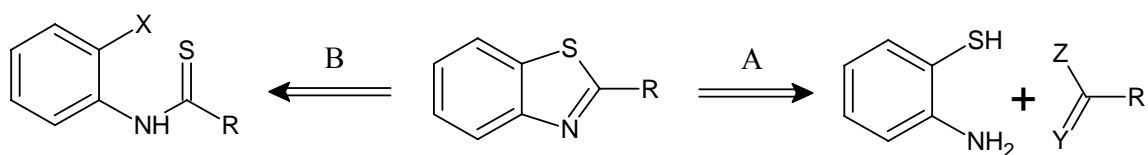
R = C₆H₅, 4-ClC₆H₄CH₂, 4-ClC₆H₄, 2,4-Cl₂C₆H₃, cyclohexyl

R' = C₆H₅, 4-CH₃OC₆H₄, 4-NO₂C₆H₄,

Scheme 59

3.1 BENZOTHAZOLES

The availability of 2-substituted benzothiazoles depends on the preparative routes in which the fused thiazole ring is constructed from acyclic reactants. The various synthetic strategies that might be adopted for the construction of a benzothiazoles moiety are depicted in (Scheme 60).



X = H, Cl, Br, I, SMe; **Y** = O, Se

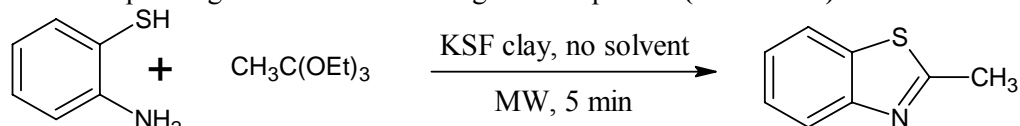
Z = H, OH, OR, NH₂

R = alkyl or aryl

Scheme 60

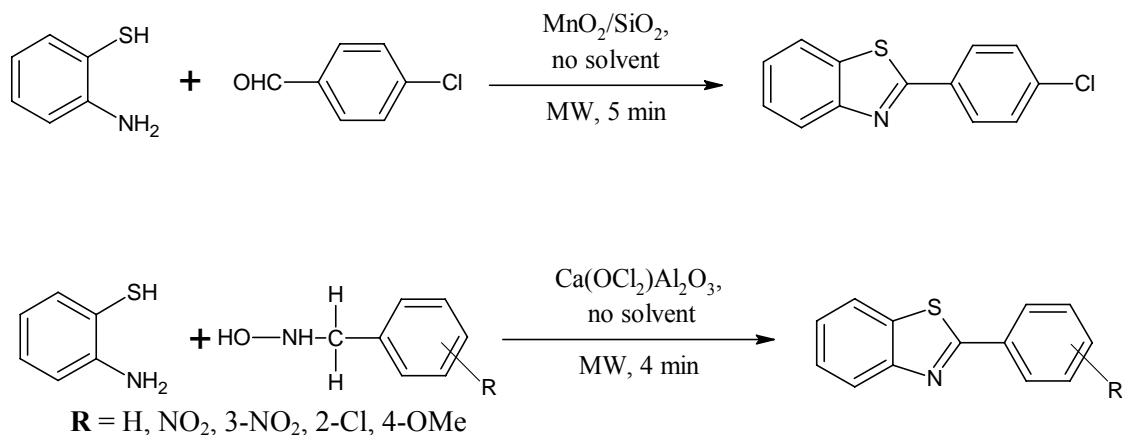
Benzothiazoles were obtained by a direct cyclocondensation of 2-aminothiophenol with a variety of carboxylic acids in the absence of any catalyst or dehydrating agent. However, some of these methods suffer from one or more of the disadvantages such as high thermal conditions, long reaction time, sometimes require excess of reagents and use of toxic metallic compounds that result in waste streams. Although direct comparison with the conventional thermal conditions was not made, reported literature precedents employed oil-bath heating of aminothiophenol with carboxylic acid at 220 °C for 4 hours in the presence of polyphosphoric acid⁷⁶ or P₂O₅ – MeSO₃H (70 °C, 10 h)⁷⁷. Consequently, the microwave methodology rendered clear advantages both in terms of reaction speed and milder conditions.

One of the published microwave-assisted synthesis of benzothiazoles is the condensation of a dinucleophile such as 2-aminothiophenol, with an *ortho*-ester in the presence of KSF clay in a monomode microwave reactor operating at 60W under a nitrogen atmosphere⁷⁸ (Scheme 61).

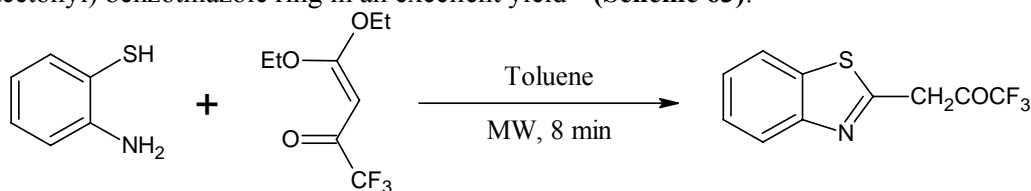


Scheme 61

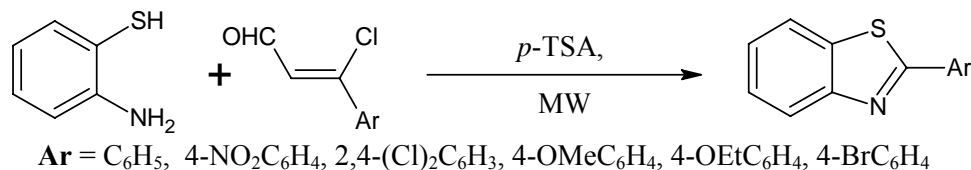
Solvent-free microwave-assisted syntheses of benzothiazoles were also described by attack of the dinucleophiles on benzaldehydes and benzaldoximes⁷⁹ (Scheme 62).

**Scheme 62**

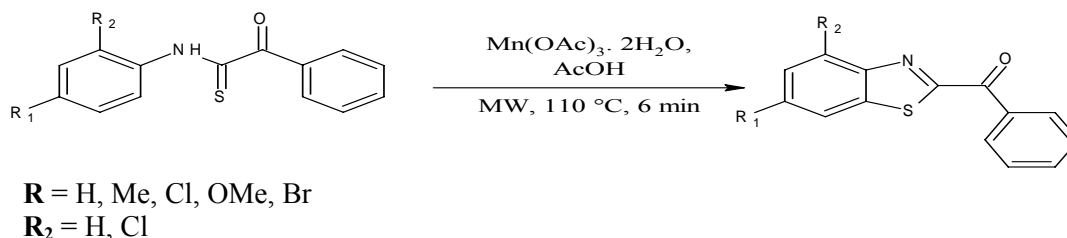
Following a similar strategy, trifluoroacetyl ketene diethyl acetal was successively condensed with 2-aminothiophenol in the presence of toluene in a multimode microwave oven to give the 2-(1,1,1-trifluoroacetyl) benzothiazole ring in an excellent yield⁸⁰ (**Scheme 63**).

**Scheme 63**

Condensation of 2-aminothiophenol with the β -chlorocinnamaldehyde in the presence of *p*-toluene sulphonic acid (*p*-TSA) gave moderate yield of benzothiazoles⁸¹ (**Scheme 64**).

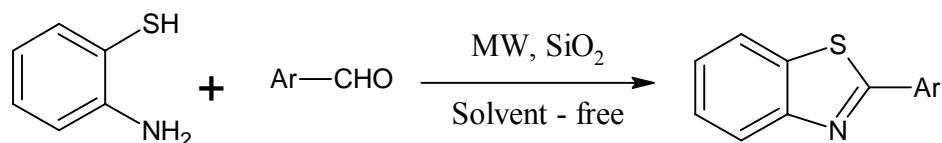
**Scheme 64**

Manganese (III)-promoted radical cyclization of arylthioformanilides and α -benzoyl thioformanilides is a recently described microwave-assisted example for the synthesis of 2-arylbenzothiazoles and 2-benzoylbenzothiazoles⁸² (**Scheme 65**). In this study, manganese triacetate is introduced as a new reagent to replace potassium ferricyanide or bromide. The 2-substituted benzothiazoles are generated in 6 min at 110 °C under microwave irradiation (300 W) in a domestic oven with no real control of the temperature (reflux of acetic acid). Conventional heating (oil bath) of the reaction at 110 °C for 6 h gave similar yields.

**Scheme 65**

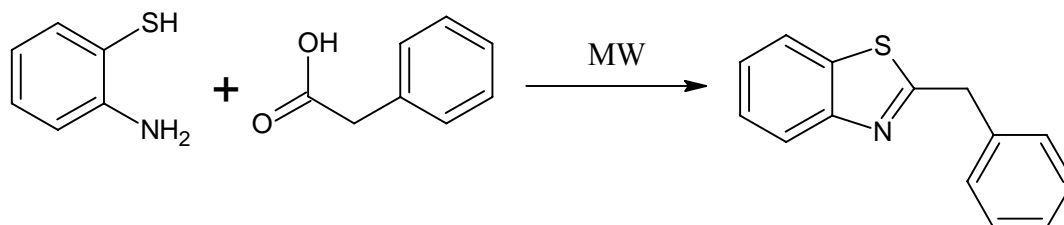
Recently, some methods use microwave heating for the synthesis of 2-substituted benzothiazoles such as condensation of aromatic or aliphatic aldehydes with 2-aminothiophenol on SiO₂⁸³ (**Scheme 66**), aromatic

aldehydes with 2-aminothiophenol in the presence of nitrobenzene/SiO₂ or nitrobenzene/ montmorillonite K10⁸⁴, or carboxylic acids⁸⁵ (Scheme 67).



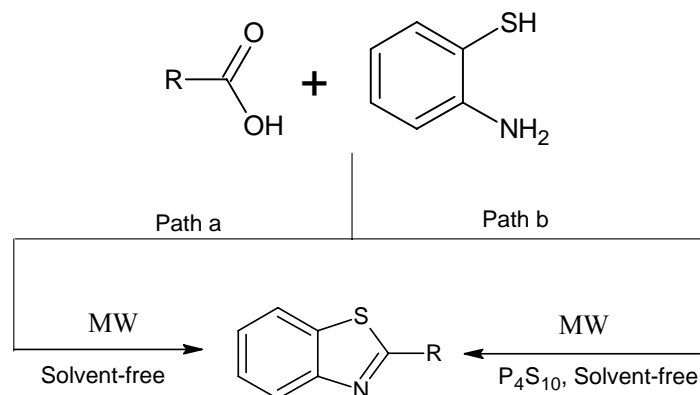
Ar = C₆H₅, 4-NO₂-C₆H₄, 3-NO₂-C₆H₄, 4-Cl-C₆H₄, 3-Cl-C₆H₄, MeOOC-C₆H₄, 4-CN-C₆H₄, 4-OH-C₆H₄

Scheme 66



Scheme 67

Recently we have also synthesized 2-substituted benzothiazoles under solvent-free microwave-assisted conditions⁸⁶ (Scheme 68).



R = long-alkyl and alkenyl chain

Scheme 68

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