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REVIEW ARTICLE

Microwave-assisted Chemical Reactions

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Microwave (MW) radiation has been used in chemical analysis and chemical synthesis. MW heating under controlled conditions offers distinct advantages over conventional heating. The reactions are carried out in environmentally clean and safe solvents and in many cases, reactions can be carried out under solvent-free conditions. This method of synthesis has grown rapidly and found its use in various sectors. This paper reviews some of the reactions that have been accelerated with higher yields under MW irradiation. The application of MW-assisted synthesis in the medicinal and pharmaceutical industries will be emphasized.

Keywords: microwave irradiation; microwave-assisted synthesis; organic synthesis; pharmaceutical; organic reaction

1 Introduction

Microwave (MW) has been applied in various fields and processes such as heating, sintering, drying, waste treatments, etc. In the medicinal industry, MW has been used in various applications including breast cancer detection in humans, (1, 2) clinical MW thermotherapy, (3) and proteomics (4).

Recently, MW technology has also developed rapidly in the field of chemical analysis and synthesis, and become an important component in combinatorial and Green Chemistry. Particularly, MW synthesis has been applied in various fields such as chemicals, pharmaceuticals, medical and biotechnology. Compared with conventional heating such as oil-bath heating, MW-assisted heating under controlled conditions has been shown to be an advanced technology in reducing reaction time, typically from days or hours to minutes, besides increasing product yield and purity. Majority of the time, hazardous and toxic solvents are used in conventional heating. In contrast, MW heating usually employs reusable reaction media and eco-friendly solvents, or even under solventless conditions. As a consequence, not only the problem of pollution can be overcome (5), but the risk of overpressure and explosions can also be avoided.

The MW synthesis technology was started in 1986 by two different groups of researchers (6, 7). Thus, it can be seen that this field is still new. However, a great deal of improvements have been achieved especially on the reactors and the techniques used. The invention of commercial MW equipment and modification of ovens that are temperature and pressure controllable have attracted the interest of chemists in this field. During the1990's, several additional features of MW synthesis were observed. A number of experiments have shown that MW radiation is capable of heating solvents above their normal boiling points, a phenomenon known as superheating. A feature of selectivity in the chemical reaction under MW irradiation was discovered by Stuerga et al. who observed that the bonding of the sulphonic acid group, which was added to naphthalene under MW irradiation, could be controlled to select the reaction for 1-naphthalene sulphonic acid (1-NSA) or 2-naphthalene sulphonic acid (2-NSA) (8). This selectivity pattern is useful in numerous reactions.

MW-assisted organic reactions using domestic or commercial ovens, basically known as MORE (Microwave Induced Organic Reaction Enhancement) Chemistry (9), is increasingly important. The MW-assisted chemical synthesis encompasses the syntheses of organic materials, organometallic compounds, coordination compounds, intercalation compounds, ceramic products, polymer products, solid-state compounds, and radiopharmaceuticals. Organometallic and coordination compounds are produced by generating covalent bonds between organic compounds and metals. Organometallic compounds are important constituent of

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vitamins whereas coordination compounds are important in medical science, besides other applications. Intercalation compounds consist of organic or organometallic compounds that are incorporated between layers of oxides and sulphides. In radiopharmaceuticals, radioisotopes are used in drug making using MW irradiation.

A large number of MW-assisted organic reactions have been carried out. These include the Diels-Alder reaction, racemization of large organic molecules through Diels-Alder cyclo-reversions, the Ene reaction, Heck reaction, Suzuki reaction, Mannich reaction, hydrogenetion of β-lactams, hydrolysis, dehydration, esterification, cycloaddition reaction, epoxidation, reductions, condensations, protection/deprotection, cyclisation reaction, etc. An extensive review of these reactions has been given by Kappe (10).

Not all materials can be used in MW chemistry. Only materials that absorb MW radiation can be used in MW synthesis. Heat is generated mostly through dipolar polarization, although conduction mechanism and interfacial polarization are possible. In polar molecules, heat is generated via dipolar polarization. The frequency of MW is most suitable to enable the occurrences of oscillations between polar particles and the inter-particle interactions in polar solution. The particles in these situations will attempt to align themselves in phase with the field. However, the particles can only move locally in random fashion due to the resisting forces generated from the inter-particle interaction. Heat is thus produced. The interactions will not affect the structure of the organic molecule since the energy of MW is too low to disrupt the molecular bond.

Many chemical reactions under MW irradiation condition are actually impossible under the conventional heating methodology. For instance, Abramovich and Bulman studied the Fischer cyclization of piperidine-2,3-dione 3-p-nitrophenylhydrazone with formic acid which leads to the corresponding β-carboline (11). They found that this leads to 72% yield under MW irradiation. However, this reaction was ineffective under classical heating. Huber and Jones also observed that the Claisen rearrangement of a series of allylic alcohols and triethyl orthoacetate is impossible under classical heating, but it occurred in 66–100% yields under solventless conditions with MW irradiation and montmorillonite-KSF catalyst (12).

Several theories have been proposed to explain the rate acceleration caused by MWs. Whittaker and Mingos believe that non-thermal effects exist in MW-assisted organic synthesis (13). However, Kappe asserts that there are no general non-thermal effects and he attributes the rate acceleration to superheating of solvents above their boiling points (14). On the other hand, the rate acceleration in solid-state catalytic reactions is considered to be attributed to high temperature in the surface of the catalyst.

The rate acceleration of MW effects on chemical reaction can be shown by the Arrhenius law relating temperature and time:

$$k = A \exp(-E/RT) \tag{1}$$

where the pre-exponential factor A depends on the frequency of vibration of the atoms at the reaction interface, and thus it can be affected by MW radiation. An increase by a factor of 3.3 in this factor causes the acceleration of the reaction rate under the MW

This article explores some of the applications of MW in chemical reactions. We focus on the chemical synthesis, particularly in the fields of biological science, medical and pharmaceutical.

2 Features and Applications of Mw-Synthesis

2.1 Eco-friendly Environment

Avoiding organic solvent during the reactions in organic synthesis is important in leading to a safe, clean, efficient and economical environment. Due to these advantages, there is an increasing interest in the use of environmentally benign reagents and procedures. Organic reactions in aqueous media have become of great interest as water is not only more environmentally friendly, but also because water often displays unique reactivity and selectivity as a solvent for organic reactions. Some organic materials have been synthesized by using the hydrophobic effects of water. Chemical processing in water is also possible under superheated conditions in sealed vessels. Specifically, water in the near-critical region at temperatures between 200 and 300°C has been employed by some researchers in organic synthesis. Employing a multimode MW reactor, Kremsner and Kappe had performed various transformations in near-critical water in the range of 270–300°C, under MW irradiation (15). These transformations include hydrolysis of esters or emides, hydration of alkynes, Diels-Alder cycloadditions, pinacol rearrangements, and the Fischer indole synthesis.

Another eco-friendly environment is achieved by the use of hydrotopes, such as arene sulphonates. These compounds are readily soluble in water, and the solution is non-inflammable and non-toxic as water is the bulk medium. In a study, Khadilkar et al. used the aqueous hydrotrope solution in MW cavity to synthesize Hantzch ester, scaled up to 75 g (16). High yields of dihydropyridines were obtained by them.

Now there is an increasing trend of using MW irradiation in synthesis under solvent-free conditions. These procedures are very attractive due to the high yields and short reaction time in the absence of solvents. Shaabani et al. synthesize 1,4-diketo-pyrrolo[3,4-*c*]-pyrroles' derivatives using MW irradiation under solvent-free conditions and it was observed that the reaction times were considerably reduced (17). Marrero-Terrero and Loupy have synthesized 2-oxyzolines from carboxylic acids and α,α,α-tris(hydroxymethyl)-methylamine using MW irradiation under solventless conditions (18). MW-assisted synthesis of 1-aminoalkyl phosphonates under solvent-free conditions has been performed by Kaboudin and Nazari (19). Olsson et al. (20) synthesize thiomides by using MW irradiation under solvent-free conditions. Through the cycloisomerization of an aldimine intermediate under MW-enhanced solvent-free conditions, Yadav and Rai used one-pot montmorillonite K-10 clay as the solid support to perform a three-component reaction of substituted salicylaldehydes, ribosyl/deoxyribosylureas and ammonium acetate to yield N-nucleosides, 4-amino-3,4-dihydro-3-(β-D-ribo- or β-D-2′-deoxyribofuranosyl)-2*H*-benz[*e*]-1,3-oxazin-2-ones (21).

Varma et al. performed most of the MW-assisted organic syntheses under solvent-free conditions. Some of the compounds which have been synthesized by them include: (a) imines and enamines (22), (b) chalcones and enones (23), (c) nitroalkenes (24), (d) sulfoxides (25), and (e) nitriles (26).

Solid state reactions are increasingly important in Green chemistry. MW-assisted dry reaction techniques use solid mineral as supports. Silica, alumina, clays are some of the common mineral supports suitable for MW-enhanced chemical reactions. Using dry media, Kidwai et al. have successfully synthesized a number of chemicals with high yields, including (a) 2-aminothiazoles and oxazoles (27) 2000; (b) 1,2,4-triazines (28); (c) thiadiazoles (29, 30); (d) pyrazolino/iminopyrimidino/thioxopyrimidino imidazolines (31); and (e) pyrano-pyrimidine (32). Chen et al. performed MW-assisted reduction of liquid and solid ketones using sodium borohydride without solvents (33). The reduction can be carried out efficiently with inorganic alumina support or nonmetal supports. Kumar et al. also obtained high yields by using MW irradiation to promote dehydration of aldoximes to nitriles on solid support (34).

Varma et al. have performed a number of organic syntheses under MW irradiation using supported reagents, most of which are under solvent-free conditions. These include: (a) oxidation of alcohols using clayfen (35), manganese dioxide on silica (36), alumina supported chromium (VI) oxide (37) or iodobenzene diacetate on alumina (38); (b) oxidation of sulfides to sulfoxides in clayfen (39); (c) reduction of carbonyl compounds using sodium borohydride supported on alumina (40); (d) isomerization of 2′-aminochalcones on clay (41); (e) cleavage of semicarbazones and phenylhydrazones with ammonium persulfate (42); (f) synthesis of 2-aroylbenzofurans, thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-b)thiazoles from α-tosyloxyketones (43); (g) reductive amination of carbonyl compounds using sodium borohydride on wet clay (44); (h) deacetylation of benzaldehyde diacetates (45); (i) regeneration of ketones from oximes on silica supported sodium periodate (46); (j) synthesis of imines and enamines using Envirocat EPZG® as catalyst (47); (k) cleavage of t-butyldimethylsilyl ethers (48); (l) synthesis of β-nitrostyrenes using clayfen and clayan (49); (m) regeneration of carbonyl compounds (50); (n) deacetylation on alumina (51); and (o) dethioacetalization of benzaldehyde diacetates (52).

2.2 Nanomaterials

MW has also been successfully applied in the synthesis of nanomaterials. Most of these materials may play an important part in pharmaceutical and medicinal sectors in the future. Wang et al. demonstrated the synthesis of cupric oxide (CuO) nanosheets and nanowhiskers by a simple MW-assisted solution methodology using $CuCl_2$ and NaOH (53), Chen et al. have also synthesized carbon nanotubes by using H_2/N_2-MW plasma (54).

Murugan et al. synthesized nanocrystalline titanium dioxide in the anatase phase using urea and $TiOCl_2$ by processing a mixture of urea and $TiOCl_2$ under MW hydrothermal conditions for 3 min. (55). X-ray diffraction studies on these powders showed the formation of single phase anatase, whereas the transmission electron microscopy investigations demonstrated that the average particle size of these powders is about 10 nm.

Spherical nanoparticles, nanosheets, polygonal nanoplates, nanorods, and nanowires were synthesized within 8 min by Tsuji et al. when they synthesized silver nanostructures using the MW-polyol method with polyvinylpyrrolidone (PVP) as a capping reagent (56). It was found that different molecular weights of PVPs produced different type of nanomaterials. When a short chain PVP (10 k) was used, nanosheets and nanoplates were dominantly synthesized, whereas nanorods and nanowires were preferentially obtained by using longer chain PVPs (40, 360 k). The authors conclude that the shape and size of silver nanostructures can be controlled by changing chain length of PVP. They also observed that the number density of silver nanostructures including spherical nanoparticles increased rapidly with increasing chain length of PVP.

Jiang et al. have successfully synthesized two types of single-crystalline Bi_2S_3 nanocrystals using Bi_2O_3, HCl, $Na_2S_2O_3$ and ethylene glycol (EG) under MW irradiation (57). The urchin-like Bi_2S_3 nanostructures were prepared using sodium dodecyl sulfate (SDS) or in the absence of any surfactant. Conversely, the Bi_2S_3 nanorods were obtained in the presence of cetyltrimethylammonium bromide (CTAB). Both urchin-like and rod-like Bi_2S_3 nanostructures were formed under MW heating at 190°C within only 30.

2.3 Biochemical Reactions

Many biochemical reactions can be accelerated via MW irradiation. Porcelli et al. performed the MW-assisted enzymatic catalysis in anhydrous media using two thermophilic and thermostable enzymes isolated from *Sulfolobus solfataricus*, S-adenosylhomocysteine hydrolase and 5′-methylthioadenosine phosphorylase (58). A non-thermal, irreversible and time-dependent inactivation of both enzymes was found after exposing these enzymes to 10.4 GHz MWs. The detection of the conformational changes of S-adenosylhomocysteine hydrolase suggests that MWs can induce protein structural rearrangements not related to temperature.

Pagnotta et al. used a modified commercial oven to perform the mutarotation reaction of α-D-glucose to β-D-glucose in the mixtures of ethanol and water as solvent at 50°C (59).

They found that the reaction was much faster, and the relative amounts of α- and β-D-glucose were different as compared to conventional heating. Bose et al. described a modified Akabori reaction that rapidly identifies the C-terminus amino acid in a polypeptide. It takes just minutes for the microwave-assisted reaction to be completed (60).

MW-promoted lipase-catalyzed reactions have been performed by several groups of researchers. Carrillo-Munoz et al. used lipases from *Pseudomonas cepacia* and *Candida antartica* for esterification and transesterification reactions at a constant temperature of around 100°C (61), Roy and Gupta performed the protease-catalyzed esterification by chymoptrypsin and transesterification by subtilisin Carlsberg in six solvents of different polarities (62). It was found that the MW irradiation accelerated the reactions 2.1–4.7 times faster than the reactions using conventional heating. Bradoo et al. also demonstrate that MW irradiation can characterize the lipase selectivities more rapidly than the conventional heating method (63).

Biswas et al. have developed a simple MW-enhanced preparation of 2-Octenyl succinic anhydride (OSA)-modified zein coating (64). They used MW to irradiate mixture of 2-Octenyl succinic anhydride (OSA) and zein in dimethyl formamide (DMF) in different concentrations. Zein is a type of cereal protein extracted in pure form and has been found in various applications including medicinal tablets, food coatings and biodegradable materials. The free hydroxyl and amine groups of zein were found reacted with OSA within 5 min under MW-assisted conditions. In another study, Maugard et al. use MW irradiation to synthesize galactooligosaccharides from lactose by using Kluyveromyces lactis-galactosidase (65). The reactions were 217 times faster by using MW irradiation.

2.4 MW Synthesis of Chemical Compounds in Medical and Pharmaceutical Industry

MW-assisted chemical synthesis plays an important part in medicinal chemistry and pharmaceuticals such as drug discovery. Investigation into the possibility of using MW irradiation to accelerate the rate and increase the yield of drug has been performed, especially drugs which are difficult to be prepared by using conventional methodology.

Acyl sulfonamide is important in medicinal chemistry as carboxylic acid bioisosteres. Wu et al. demonstrated that acyl sulfonamides, which act as carboxylic acid bioisosteres in medicinal chemistry, can be synthesized from both aryl iodides and aryl bromides by direct carbonylation using MW irradiation (66). Molybdenum hexacarbonyl was used as the carbon monoxide source. These authors have also synthesized a potent hepatitis C virus NS3 protease inhibitor comprising acyl sulfonamide elements by using MW irradiation.

MW radiation has also been applied successfully in the synthesis of heterocyclic compounds which are important in medicinal. For instance, Varma and Dahiya had synthesized 2-amino substituted isoflav-3-enes by using MW irradiation (67). Varma et al. has synthesized flavones, which are useful in disease treatment via MW irradiation of o-hydroxydibenzoylmethanes intermediates adsorbed on montmorillonite K10 clay for 1–1.5 min under solvent-free condition (68). An important compound in pharmacology, benzo[b]furans, can be synthesized by using MW dielectric heating. For instance, 2-aroylbenzofurans has been synthesized successfully by the condensation of α-tosyloxyketones with salicylaldehydes on potassium fluoride ‘doped’ alumina (43). In another study, Varma and Saini had synthesized tetrahydro-4-quinolones using MW irradiation and montmorillonite K10 clay (41). These chemicals are important precursors for several medicinally important compounds. Another chemical, thiazoles, which are of pharmacological importance, can be obtained from ethylenethioureas and α-tosyloxyketones in clay-catalyzed solid state via MW heating (43). Boufatah et al. also carried out MW-assisted synthesis of new sulfonylbenzimidazole-4,7-diones. These heterocyclic quinones have the potential as anti-tumor compounds (69).

Swamy et al. synthesized *N*-alkylated benzotriazole derivatives which are pharmaceutically important bioactive substituents (70). The compounds were synthesized by *N*-alkylation of the benzotriazole with different bioactive alkyl halides in the presence of powdered K_2CO_3 in DMF solution under MW irradiation resulted in good yield compared to the conventional method.

Dandia et al. have synthesized heterocyclic compound 2,3-disubstituted quinazolin-4 (3*H*)-ones by a neat three component cyclocondensation of anthranilic acid, phenyl acetyl chlorid/benzoly chloride and substituted anilines under MW irradiation (71). Quinazoline compounds have been used to treat leprosy and mental disorders. These compounds are also important as antifungal and central nervous system depressants, as well as AMPA inhibitors. Dandia et al. have also synthesized other important compounds, such as pyrazolo [4,3-c](1, 5)-benzothiazepines which are important in pharmacology as calcium channel blockers, and have been used as ingredients in *Diltiazem* (72).

Phthalocyanines, which can be used as sensitizers for photodynamic cancer therapy, have been synthesized by some researchers. A monomode MW reactor with an accurate temperature control feature was used by Burczyk et al. to synthesize phthalocyanines under solvent-free conditions using 1,2-phthalonitrile or phthalic anhydride and urea as substrate, and cobalt (II) chloride hexahydrate and copper (II) chloride dihydrate as templates (73). As compared to conventional heating, reduction of time and higher yields were observed in MW heating.

Walla and Kappe employed microwave-assisted Negishi and Kumada cross-coupling reactions with palladium as catalysts to synthesized aryl chlorides, compounds found in pharmaceuticals and natural products (74). They found that the optimal conditions to achieve the highest yields was 175°C for 10 min. In another study, Mu et al. synthesized

α-amino phosphonates, which are used as anti-tumor, antihypertensive and antibacterial agents (75). By using a MW-enhanced catalysts-free and solvent-free three-component Kabachnik-Fields reaction, the reaction process which involved aldehyde, amine, and dimethyl phosphite completed at a temperature of 80°C in 2 min with a 98% yield.

Molteni et al. used MW irradiation converse enaminoketones formed *in situ* into a variety of heterocycles by reaction with the appropriate bidentate nucleophile (76). They synthesized various important compounds, such as pyrazoles, pyrimidines and isoxazoles by using a one-pot procedure in aqueous media. These compounds are used in the medicinal and pharmaceutical fields. Dihydropyridine is an important calcium channel blocker (77, 78). The pyrimidines and pyridine family and their derivatives are important in biological functions, and have also been synthesized by other researchers such as Bagley et al. (79, 80). The indazoles, pyrazolopyridines and bipyrazoles that are useful as anti-inflammatory drugs have also been synthesized using MW irradition via cycloaddition reactions under solvent-free conditions (81).

Kidwai et al. have synthesized a number of new antibacterial compounds, including (a) quinolones (82, 83); (b) cephalosporin derivatives (84–87) and (c) beta-lactam. (88, 89) Kidwai et al. have also synthesized a number of fungicidal compounds, such as: (a) organomercurials of benzoquinone, barbituric acid and thiobarbituric acid (90–93); and (b) pyzaloes (94). Some other important antimycobacterial agents, such as 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole analogues have been synthesized by Bhaumik and Akamanchi (95).

Using basic alumina as solid support, Dandia et al. synthesized a new class of fluorine containing 3-alkyl-7-chloro-11a,12-dihydro-11-phenyl-12-(substituted aryl)-11*H*-benzopyrano[4,3-*e*)[1,2,4)-triazolo[3,4-*b*)[1,3,4)-thiadiazepines from 4-amino-5-alkyl-3-mercaptotriazole and substituted 3-arylidene flavonones under MW irradiation (96). They found that the reaction time was 3–5 min under MW irradiation whereas it took 60–65 h under conventional heating. The compounds synthesized have good anti-fungal properties. which have shown their effectiveness against pathogens such as *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici*.

3 Conclusions

The application of MW methodology to chemical synthesis has opened up new opportunities for the synthetic chemists by providing novel routes not practical by conventional methods. MW assisted reactions are found to be rapid, efficient and safe. The approach is eco-friendly and this pollution preventive strategy is now an important part of modern combinatorial and Green Chemistry.

In conclusion, recent synthetic studies on various processes by utilizing MW irradiation have shown the high potential of MW irradiation in obtaining high yield products. The experimental procedures are simple and the processes are environmentally benign. More research should have been performed to explore more novel chemical compounds which can be synthesized under MW-assisted methodology but cannot be obtained by conventional method.

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