Microwave assisted organic reaction as new tool in organic synthesis

A K Nagariya 1, A K Meena 1, Kiran2, A K Yadav 1, U S Niranjan 1, A K Pathak 1, B Singh 2 and M M Rao 1

1National Institute of Ayurvedic Pharmaceutical Research, Patiala – 147001, Punjab, (India)
2School of pharmaceutical sciences, Shobhit University, Meerut, U.P. (India)

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ABSTRACT

Microwave assisted organic synthesis (MAOS) has emerged as a new “lead” in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now day’s technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.

Keywords: Microwave irradiation; MAOS; Green Chemistry; Yield, Lead, Reduction.

INTRODUCTION

Microwave-assisted organic synthesis has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes 1. Microwave (MW) irradiation, an unconventional energy source, has been used for a variety of applications including organic synthesis, wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules 2. Also we have described Microwave irradiation produces efficient internal heat transfer (in situ heating), resulting in even heating throughout the sample as compared with the wall heat transfer that occurs when an water/oil bath is applied as an energy source 3. Many applications of microwaves, as an efficient heating source for organic reactions, have been reported in the literature 4. The microwave assisted reactions occur more rapidly, safely and with higher chemical yields 5. Microwave-assisted organic synthesis (MAOS) is now entering the new technologies arena as a tour de force in process, medicinal and combinatorial chemistry. We hope to demonstrate in this review the utility of this technique, and the potential that this methodology can give to the bench chemist 2. The chief features of the microwave reactions are the enhanced selectivity, much improved reaction rates, milder reaction conditions and formation of cleaner products 6.

MICROWAVE HEATING

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. This form of heating has been used in the rapid heating of foodstuffs for more than 50 years. However, the advantages of using microwave dielectric heating for performing organic transformations have only emerged since the mid-1980s. This technology opens up new opportunities to the synthetic chemist, in the form of new reactions that are not possible using conventional heating, improved reaction yields, decreased reaction times and even solvent-free reaction Conditions 7. Developments in this field have suggested that microwave-assisted chemistry could be used in most reactions that require heating 8.

MICROWAVE THEOREY

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radiowave. Microwaves have frequencies between 0.3 GHz and 300 GHz, corresponding to wavelengths between 1 mm and 1 m, respectively virtually all domestic and commercial equipment today uses a frequency of 2.45 GHz (wavelength 12.2 cm) for operation 9. When comparing the ability of different solvents to interact with microwave radiation, two important considerations are (1) the solvent’s ability to absorb micro-
wave energy and (2) its ability to convert the absorbed energy into heat. The interaction of a solvent with microwave irradiation is highly complex. As well as being dependent on the solvent’s dielectric properties, which are in turn dependent on the temperature of the solvent and the frequency of the applied radiation, the interaction is also dependent upon the viscosity of the solvent (which is also temperature dependent). The best approximation for the comparison of different solvents is to compare their loss tangent values. The loss tangent (\(\tan\delta\)) is defined as the tangent of the loss angle (\(\delta\)), which is the ratio between the dielectric constant, \(\varepsilon'\), and the loss factor, \(\varepsilon''\). (which quantifies the efficiency with which the absorbed energy is converted to heat)

\[
\tan\delta = \frac{\varepsilon''}{\varepsilon'}
\]

The dielectric constants of acetone and ethanol, for example, are indeed in the same range, but ethanol has a much higher loss tangent. or this reason, ethanol couples better with microwave radiation, resulting in a faster temperature increase. Apart from the importance of the physical properties of the sample itself, the actual geometry and volume of the sample (load) are crucial to provide uniform and reproducible heating\[1\]. When the dielectric properties of the sample are too poor to allow efficient heating by microwave radiation, the addition of small amounts of additives (e.g. ionic salts) that have large loss tangent values can significantly overcome these problems and enable adequate heating of the whole mixture. This often provides an efficient way of using nonpolar solvents for running syntheses using microwave radiation. However, solubility problems can result in heterogeneous mixtures that might cause problems in syntheses because of different degrees of heating. Fluid salts, or ionic liquids, consist entirely of ions and therefore absorb microwave radiation in a highly efficient manner. Many ionic liquids are particularly attractive additives because they are relatively inert, are stable at temperatures up to 200°C and have a negligible vapour pressure\[12, 13\]. It now appears to be accepted that the different temperature regime caused by microwave dielectric heating is the main contributing factor to any rate acceleration observed in MAOS\[11, 14, 15\].

**MICROWAVE-ASSISTED ORGANIC SYNTHESIS IN DRUG DISCOVERY:**

Nowadays, MAOS is gaining widespread acceptance in drug discovery laboratories. The rapid acceptance of this technology parallels the rising cost of R&D and decrease in the number of FDA approvals, which have led to what is termed as a productivity crisis. Reducing the cost of failure, either by failing candidates sooner or by improving the overall probability of success, is the most powerful solution to improving R&D productivity. Microwave technology, by accelerating chemical reactions from hours or days to minutes, provides quick results. From time to time microwave heating enables chemistries that were not previously possible by classical methods\[16\].

**LEAD OPTIMIZATION**

MAOS is also starting to make an impact on medicinal chemistry. Kappe et al. have prepared the kinesin Eg5 inhibitor, monastrol, under microwave conditions, By using a microwave-assisted Biginelli reaction they achieved a higher yield of the inhibitor with an improved purity profile, compared with the conventional synthesis method\[17\]. Kidwai et al. have shown microwaves to be effective in the synthesis of the novel antibacterial \(\beta\)-lactams\[18\], quinolines\[19\], and cephalosporins\[20\]. The synthesis of anticarcinogenic soybean isoflavones\[21\]. The antileukaemic alkaloid, convolutamydine-A\[22\], and the nitrogen mustard \(\beta\)-lactams and indoles\[23\], have also been reported to be enhanced by microwave irradiation. Hallberg et al. have described the use of microwave promoted couplings in their ‘fast synthesis’ of modified HIV-1 protease inhibitors. The palladium-catalyzed coupling of commercially available aryl and heteroarylboronic acids was affected by microwave irradiation, enabling the synthesis and isolation of the desired compounds in high yields\[24\]. Ley and his group\[25\], have demonstrated the effectiveness of combining polymer-supported synthesis with microwave-assisted organic chemistry in the clean and efficient synthesis of the well-known commercially important pharmaceutical drug, sildenafil (Viagra™).

**DRUG DEVELOPMENT:**

The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when classical methods require forcing Conditions or prolonged reaction times. Where processes involve sensitive reagents or there is a possibility of compound decomposition under prolonged reaction conditions, microwaves have also shown an advantage. The use of focused microwave radiation to decrease reaction times and improve yields has recently been demonstrated in the multi-step synthesis of a thiazolo[5,4-\(f\)]quinazoline\[26\]. In contrast to conventional heating, using focused microwaves (irradiation in solution, 300 W) gave the desired compounds in higher overall yield with shorter reaction times and products that are more amenable to purification. An interesting application of microwave activation is the epimerization of optically active compounds. A wide range of amino acids has been epimerized quantitatively within two minutes, thus avoiding the considerable decomposition that is associated with the use of classical heating\[27\].

**SOLVENT-FREE SYNTHESIS:**

In the past, MAOS has been carried out under dry or solvent-free conditions, mainly to avoid the hazards of using volatile and flammable organic solvents in domestic microwave ovens. Although the solvent-free technique claims to be environmentally friendly, as it avoids the use of solvents, this is debatable because solvents are often used to pre-absorb the substrates onto, and wash the products off, the solid supports. For neat solids, it is very difficult to obtain a good temperature control at the surface of the solids and local hot spots might be encountered. This can sometimes give rise to unexpected results and inevitably lead to problems regarding reaction predictability, reproducibility and control. For some reactions requiring high temperatures, however, the presence of microwave-absorbing solids can be advantageous. For instance, the best procedure\[28\], for the preparation of bis-quinazolin-4-ones was found to be via a microwave-assisted Niementowski reaction, whereby a mixture...
of the starting amidine and an excess of anthranilic acid, were heated at 220 °C, in the presence of graphite. The sealed vials allowed high temperatures to be reached and prevented sublimation of the anthranilic acid. This reaction, when performed in the presence of solvents, such as N-methylpyrrolidinone (NMP) or N,N-dimethylformamide (DMF), offered only 37% product and a large amount of byproducts. Neat reactions of liquid substrates can be quite successful. For example, the addition of P (O)–H bonds to alkenes has been accomplished using microwave irradiation in the absence of added solvent or catalyst. Tandem hydrophosphinylation reactions with alkynes afforded unsymmetrical species such as phosphine oxide and phosphonates.

**EFFECT ON PROCESS DEVELOPMENT**

Microwave-assisted organic synthesis is beginning to play a greater role in process development, especially in cases where classical methods require prolonged reaction times and forced conditions. Continuous and batch microwave reactors have been constructed for efficient, ‘green’ synthesis with low-boiling solvents at high temperatures in closed vessels. Commercial microwave systems based on these developments are available.

**LITERATURE SURVEY:**

Various review published on the microwave assisted organic synthesis, and well focused on the potential of the MAOS, one of them Lidström, P. et al. (2001) published a review on Microwave-assisted organic synthesis, they abstracted a number of microwave assisted organic synthesis from the literature those published from 1994 to June 2000. In the our review study survey of microwave assisted synthesis is abstracted from the literature published from 1999 to 2009 (Sep.). After survey of various literature it was confirmed that number of reaction has been performed by applying microwave irradiation method like N-acylation, alkylation, condensation, esterification and transesterification, cyclodiation, deprotection and protection, oxidation, reduction, dehydration, dehalogenation, rearrangement. Some of the important MAOS are given here.

1. In the year 2009 (Sept.) Aniket K. Shirsagar, Mrunmayee P. Toraskar, Vithal M. Kulkarni, Shweta, Dhanashire, Vilasrao Kadam. Synthesized and evaluate antiinfective and anticonvulsant activity of thiosemicarbazones derivative 5-mercaptop-3-(3’-pyridyl)-4H-1,2,4-triazole-4, by MAOS.

2. In the year 2009 (July). Kiran F. Shelke, Suryakant B. Sapkal, Nana V. Shiite, Bapu Rao B. Shingate, Murlidhar S. Shingar. synthesised 1-benzoxazole derivatives in ionic liquid under microwave irradiation condition.

3. In the year 2009 Yu Chen, Nataliya A. Markina, Richard C. Larock synthesized indoles under Sonogashira conditions by microwave-assisted, one-pot synthesis.

4. In the year 2008 (Dec). Prasad K. K., Toraskar M. P, Kulkarni V.M and Kadam V. J., Synthesized and evaluate Antifungal activity of Schiff’s bases of Benzotriazolyl - 4-amino -1, 2, 4 triazoles by MAOS.

5. In the year 2008 (July) Rastogi sameer, and Pathak devender. Synthesized and evaluate antimicrobial activity of, N-aryl-2,3-(3’-oxo-1,4-benzothiazin-2’-y1) acetamide derivative. under microwave irradiation condition.

6. In the year 2008 Kahveci, B.; Ozil, M.; Serdar synthesized some 1,2,4-triazol-5-one derivatives, under microwave irradiation condition.


8. In the year 2007 (Dec.) Shindalkar, S. S.; Madje, B. R.; Shingare, M. S. Synthesized Microwave induced protection and deprotection of 4-oxo-(4H)-1-benzopyran-3-carbaldehydes.


11. In the year 2007 Nicolas Wlodarczyk, Pauline Gilleron, Re’gis Millet, Raymond Houssin and Jean-Pierre He ‘nicht.synthesized 1,4-diazepin-5-ones under microwave irradiation and their reduction products.

12. In the year 2006 (March) Shou-Yuan Lin, Yuko Isome, Ethan Stewart, Ji-Feng Liu, Daniel Yohannes and Libing Yu. was developed One-pot synthesis of benzimidazoles from diamines and carboxylic acids under microwave irradiation condition.


15. In the year 2005 Park sang hyun, Gwon hui jeong, Lee Hyo sun, and Park kyung bae synthesized aryl piperazine derivatives, for imagine 5-HT receptor under microwave irradiation.

16. In the year 2005 S. Chandrasekaran, S. Nagarajan synthesized and evaluated anti-bacterial activity of some 2-Amino-6-aryl-4-(2-thienyl)pyrimidines. under microwave irradiation condition.

17. In the year 2005 Aouregan M. Jacob and Christopher J. Moody synthesised 2,1-disubstituted-1,4-benzoxquinone natural products microwave irradiation condition.


19. In the year 2002 Karale, B. K.; Chavan, V. P.; Mane, A. S.; Millet, Raymond Houssin and Jean-Pierre He’nicht synthesized Schiff’s bases of Benzotriazolyl - 4-amino -1, 2, 4 triazoles under microwave irradiation condition.

CONCLUSION AND FUTURE TRENDS MICROWAVE

One of the biggest tasks facing the pharmaceutical companies is to accelerate drug development by increasing productivity, discovering new leads, and generating novel therapeutic agents against the vast numbers of potential drug targets. The goal of the medicinal chemist is to develop leads efficiently to identify strong candidates early so as to minimize failure rate of compounds in clinical trial and move drugs into the marketing pipeline quickly. Rapid lead generation and optimization has recently been facilitated by the emergence of MAOS and the technique is today one of the major tool for the medicinal chemist. MAOS is undoubtedly going to play a major role in chemistry development; this is substantiated by the fact that in most pharmaceutical and biotechnology companies microwave synthesis is the vanguard methodology today. Now days it could be considered that all of the previously, conventionally heated reaction could be performed using this technique. Example presented in the section literature survey are impressive and provide a brief knowledge about work done on the field of organic synthesis with the application of microwave assisted synthesis.

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