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MICROWAVE MEDIATED SYNTHESIS IN PHARMACEUTICAL CHEMISTRY

Chanti Babu Patneedi*, Durga Prasadu K., R. S. K. Sharma, D. Chandra Sekhar and D.V. Venkata Rao
Visakhapatnam, A.P.-530041, India
*E-mail: chantibabu.chem@gmail.com

ABSTRACT
The application of microwaves as an efficient form of volumetric heating to promote organic reactions was recognized in the mid-1980 s. It has a much longer history in the food research and industry where microwave irradiation was studied in depth to optimize food browning and the development of synthetic reactions. Microwave organic synthesis opens up new opportunities to the synthetic chemist in the form of new reaction that are not possible by conventional heating and serve a flexible platform for chemical reaction. The time saved by using focused microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high-speed combinatorial and medicinal chemistry. The study presents examples that demonstrate the significance of these advantages to industrial application.
Keywords: Microwave irradiation, Synthetic methods and Pharmaceuticals.

INTRODUCTION

Introduction Revolution in organic compound synthesis has been promoted by microwave assisted methods by which small molecules are built up into large polymers in a fraction of time when compared to thermal methods ensuring the acceptance of Microwave assisted irradiation reactions as a valuable tool for acceleration of a wide variety of organic molecules development[1,2]. The advent of microwave assisted technology in organic chemistry dates back to the mid 1980s and since the 1990s there has been a significant increase in the number of publications on Microwave Assisted Organic Reactions (MAOS) [3-8] due to increased benefits associated with the process. The promotion of microwave assisted reactions in organic chemistry has improved the speed, reduced cost, reduced energy spent making it a sustainable process and is widely heralded as "green chemistry" measures[9,10] whose applications are promoted today to minimize the use of non renewable resources as well as polluting solvent, to reduce generation of secondary products which are often toxic and to reduce the emission of harmful gases[11-13]. Microwave assisted reactions in organic chemistry achieve the same by ensuring facilitation of faster reactions under bulk conditions as well as promoting reduction of reaction time[13]. The need for different organic compound libraries for drug discovery, biomaterial development, automated library screening, proteomics etc has supported the emergence of innovative technologies for rapid combinatorial organic synthesis using MAOS synthesis[7].The ability to reduce reaction time from days and hours to minutes using microwave assisted reactions has promoted advent of microwave technology in combinatorial chemistry[14,15] and drug discovery[16,17] as there is reliance on generation of large number of compounds whose production has been diversified as well as enhanced due to MAOS as there is increased production of cleaner reactions and more pure products[18,19]. Hence this article focuses on the latest advances in this area after giving a brief introduction on the Microwave process as well as the equipment used.

EXPERIMENTS

Microwave have been used to speed up chemical reactions in the laboratories[3] which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis[20].During recent years, microwaves have been extensively used for carrying out

chemical reactions and have become a useful non-conventional energy source for performing organic synthesis[21].This is supported by a great number of publications in recent years, particularly in 2003, related to the application of microwaves as a consequence of a great availability of dedicated and reliable microwave instrumentation[22-25].The first recorded application of microwave energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and methacrylic acid using pulsed electromagnetic radiation. The start of the rapid growth of microwave assisted procedures in organic synthesis was ignited in 1986 by pioneering papers by Gedye and co-workers[25] and Giguere and coworkers[26].During the last two decades, the activity in this new technique has experienced exponential growth and has been extensively reviewed[27-31].Kappe and Dallinger have reported the impact of microwaves on drug discovery[28].Even microwave-assisted reactions under solvent-free conditions promoted the synthesis of Zincke's salt and its conversion to chiral pyridinium salts in water[29] and microwave- assisted organic transformations using benign reaction media have also been reported[30, 32].Moreover, Varma and co-workers have reported the drug discovery by using aqueous microwave chemistry[29,30].

Principles of Microwave Activation

In the electromagnetic spectrum the microwave radiation region is located between infrared radiation and radio-waves[31].Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. In order to avoid interference with these systems, the household and industrial microwave ovens operate at a fixed frequency of 2.45 GHz[33-35].The energy of the quantum involved can be calculated by the Planck's law $E = h \nu$ and is found to be 0.3 cal mol–1. Presently, organic transformations take place by either of the two ways.

Conventional heating

In this method of heating, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the reacting system.

Microwave heating

Here, microwaves couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in the temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity. Only the reaction vessel contents are heated and not the vessel itself; better homogeneity and selective heating of polar molecules might be achieved. The acceleration of chemical reactions by microwave exposure results from the interactions between the material and electromagnetic field leading to the thermal and specific (non-thermal) effects. For microwave heating, the substance must possess a dipole moment. A dipole is sensitive to external electric field and tries to align itself with the field by rotation. If submitted to an alternating current, the electric field is inversed at each alterance and therefore dipoles tend to move together to follow the inversed electric field. Such a characteristic induces rotation and friction of the molecules, which dissipates as internal homogeneous heating. The electric field of commonly used irradiation frequency (2450 MHz) oscillates 4.9 × 109 times per second. Thus, microwave heating is directly dependent on dielectric properties of a substance, dielectric constant (ε') and dielectric loss (ε"). The ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature, is calculated using $\varepsilon'' / \varepsilon' = \tan \delta$ (1) where δ is the dissipation factor of the sample, ε" is the dielectric loss, which measures the efficiency with which heat is generated from the electromagnetic radiation and ε' is the dielectric constant which gives the ability of a molecule to be polarized by an electric field. The high value of dissipation factor δ indicates large susceptibility to microwave energy[36].The conduction mechanism leads, due to the much stronger interaction of ions with electric field, to the generation of heat. The ions will move under the influence of an electric field, resulting in expenditure of energy due to an increased collision rate, converting kinetic energy into heat. The heat generated by both mechanisms adds up resulting in a higher final temperature.

Since the ability of a molecule to couple with the microwave radiation is a function of its molecular polarisability (i.e. a function of its dipole moment), only polar molecules interact with microwave energy. As a guide, compounds with high dielectric constants such as water, ethanol, acetonitrile, *N,N*-dimethylformamide (DMF), acetic acid, chloroform. Dichloromethane, acetone, ethylene glycol etc., tend to heat rapidly under microwave irradiation, while less polar substances, such as aromatic and aliphatic hydrocarbons or compounds with no net dipole moment, such as carbon dioxide, carbon tetrachloride, diethyl ether etc. as well as highly ordered crystalline substances, are poorly absorbing. Thus, polar molecules in a non-polar solvent would absorb energy, but not the solvent or the reaction vessel, if it is made of Teflon (μ = 2.1 at 22 °C) or ceramic or even Pyrex (μ= 4.5–6.0). Sometimes it is possible to use mixtures comprising microwave active reactants and microwave inactive solvents. It has also been suggested that if microwave energy is absorbed by the solvent and not by the substrate, only modest rate increase will result relative to those observed with conventional energy. If, on the other hand, the microwave energy is absorbed selectively by a reactant, by a complex or by an intermediate during the rate determining step, then large rate increase will result.

Working of the Microwave Oven

In a microwave oven, microwaves are generated by a magnetron. A magnetron is a thermo-ionic diode having an anode and a directly heated cathode. As the cathode is heated, electrons are released and are attracted towards the anode. The anode is made up of an even number of small cavities, each of which acts as a tuned circuit. The anode is, therefore, a series of circuits, which are tuned to oscillate at a specific frequency or at its overtones. A very strong magnetic field is induced axially through the anode assembly and has the effect of bending the path of electrons as they travel from the cathode to the anode. As the deflected electrons pass through the cavity gaps, they induce a small charge into the tuned circuit, resulting in the oscillation of the cavity. Alternate cavities are linked by two small wire straps, which ensure the correct phase relationship. This process of oscillation continues until the oscillation has achieved sufficiently high amplitude. It is then taken off by the anode via an antenna. The variable power available in domestic ovens is produced by switching the magnetron on and off according to the duty cycle. Microwave dielectric heating is effective when the matrix has a sufficiently large dielectric loss tangent (i.e. contains molecules possessing a dipole moment). The use of a solvent is not always mandatory for the transport of heat[37].Therefore, reactions performed under solvent-free conditions present an alternative in the microwave chemistry and constitute an environmentally benign technique, which avoids the generation of toxic residues, like organic solvents and mineral acids, and thus allows the attainment of high yields of products at reduced environmental costs. This emerging environmentally benign technique belongs to the upcoming area of green chemistry.

Various Types of Microwave assisted Organic Reactions

The microwave-assisted organic reactions have been broadly classified into two categories-

1. Microwave-assisted reactions using solvents;
2. Microwave-assisted reactions using solvent-free conditions.

Microwave Assisted Reactions using Solvents

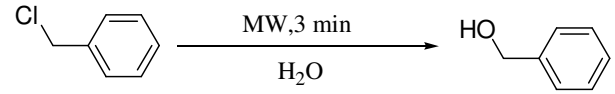
In the case of the microwave-assisted reactions using (organic) solvents, the reactants are usually dissolved in the solvent, which often couples effectively with microwaves and thus acts as the energy transfer medium. The use of aqueous media for organic reactions[38-42] is also under active investigation and temperatures of up to 100 °C and above have been employed for the syntheses[43,44,46] often intended to exploit the hydrophobic effect[45].Water has a dielectric constant 78 at 25 °C which decreases to 20 at 300 °C; the latter value being comparable with that of the solvents, such as acetone, at ambient temperature[46].Thus, water at elevated temperature can behave as a pseudo-organic solvent[51] and is a possible environmentally benign replacement for organic solvents. In addition to the environmental advantages[47,48] of using water instead of the organic solvents, isolation of the products is often facilitated by the decrease of the solubility of the organic material upon post-reaction cooling[50].An alternative

method for performing microwave assisted organic reactions, termed enhanced microwave synthesis (EMS)[49],has also been examined. By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture. In the conventional microwave synthesis (CMS), the initial microwave power is high, increasing the bulk temperature (TB) to the desired value very quickly. However, upon reaching this temperature, microwave power decreases or shuts off completely in order to maintain the desired bulk temperature without exceeding it. When microwave irradiation is off, classical thermal chemistry takes over, losing the full advantage of microwave irradiation, which is used to reach TB faster. Microwave enhancement of chemical reactions will only take place during the application of the microwave energy. This source of energy will directly activate the molecules in a chemical reaction, and therefore it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied, resulting in the significantly greater yields and cleaner chemistries. Recently, the combination of two prominent green chemistry principles, namely microwaves and water has become very popular and received substantial interest. A plethora of very recent synthetic applications describes a variety of new chemistries that can be performed with microwave irradiation but a wide range of microwave- assisted applications is still waiting[52].Many organic transformations proceed via radical chemistry. As chemists wonder if microwave irradiation can promote radical transformations, microwave-assisted free radical chemistry is increasingly being explored[53].Microwave irradiation is applicable not only to the solvent phase chemistry, but also to the solid-phase organic synthesis.

Following are the example of microwave assisted reaction using solvents-

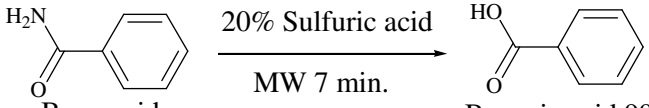
1. Hydrolysis[51]

Hydrolysis of benzyl chloride with water in microwave oven gives 97 % yield of benzyl alcohol in 3 min. The usual hydrolysis in normal way takes about 35 min.



Benzyl chloride Scheme-1 Benzyl alcohol 97%

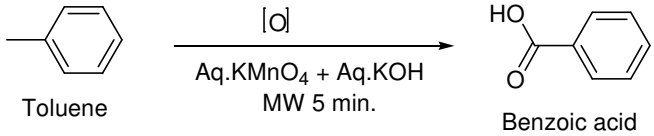
The usual hydrolysis of benzamide takes 1 hr. However, under microwave conditions, the hydrolysis is completed in 7 min giving[52] 99 % yield of benzoic acid.



Benzamide Scheme-2 Benzoic acid 99%

2. Oxidation

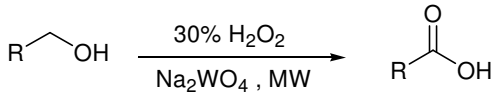
Oxidation[52] of toluene with KMnO4 under normal conditions of refluxing takes 10-12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40 %.



Toluene Benzoic acid

Scheme-3

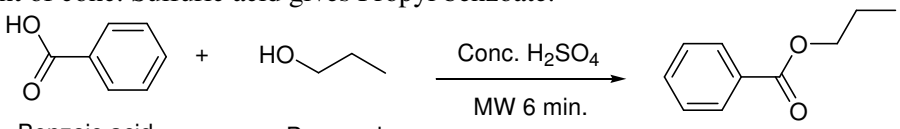
A Number of primary alcohols can be oxidized to the corresponding carboxylic acid using sodium tungstate as catalyst in 30 % aqueous hydrogen peroxide.



Scheme-4

3. Esterification[53]

A mixture of benzoic acid and n- Propanol on heating in a microwave oven for 6 min in presence of catalytic amount of conc. Sulfuric acid gives Propyl benzoate.



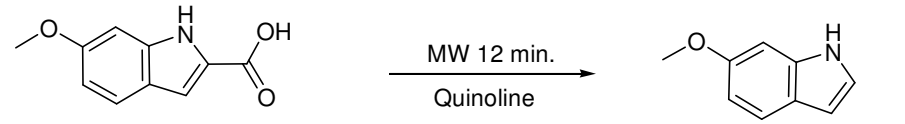
Benzoic acid n-Propanol

Scheme-5

Propyl benzoate

4. Decarboxylation[54]

Conventional decarboxylation of carboxylic acids involves refluxing in quinoline in presence of copper chromate and the yields are low. However, in the presence of microwaves decarboxylation takes place in much shorter time.



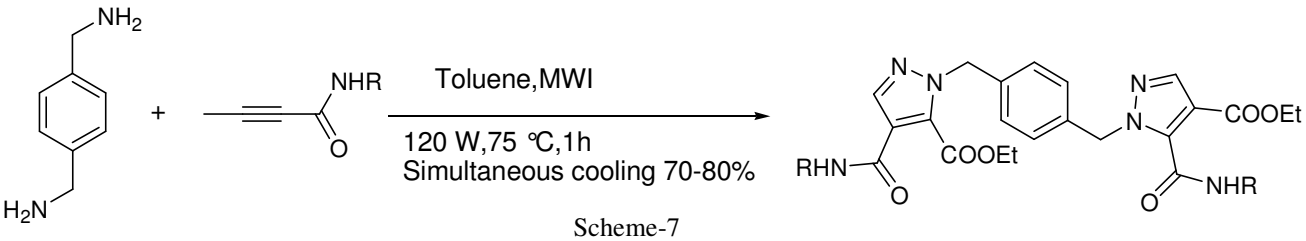
6-Methoxy-indol-2-carboxylic acid

Scheme-6

6-Methoxy-indole 99%

5. Cycloaddition

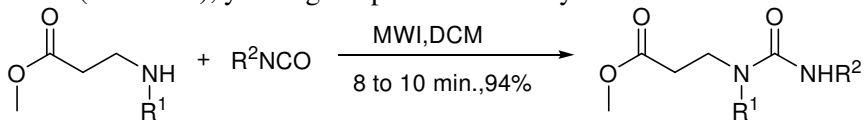
1, 3-Dipolar cycloadditions[55] are important reactions in organic synthesis. Cycloaducts were prepared by carrying out the reaction between an azide and a substituted amide in toluene. This reaction was carried out under microwave irradiation at 120 W at 75 °C for 1 h. The product was isolated in 70–80 % yield**.**



Scheme-7

6. N-Acylations[56]

N-Acylations were carried out using secondary amines and isocyanate in dichloromethane under microwave irradiation (8–10 min), yielding the product in 94% yield.



Scheme-8

Microwave assisted Reactions under Solvent-Free Conditions

Due to the environmental concerns, there has currently been an increasing demand for efficient synthetic processes and solvent-free reactions. Some old and new methodologies are being used to diminish and prevent pollution caused by chemical activities. In this context, the microwaves have become an important source of energy in many laboratory procedures.[57] Furthermore, microwave-assisted solvent-free organic synthesis (MASFOS) has been developed as an environmentally friendly process as it combines the selectivity associated with most reactions carried out under microwaves with solvent and waste-free procedures in which organic solvents are avoided throughout all stages.[58] In these environmentally conscious days, the research and development are directed towards devising cleaner

processes. Environmental hazards and the subsequent degradations are instrumental for the rapid evolution of green chemistry concept involving benign reagents and conditions.
The MASFOS reactions are of three types:

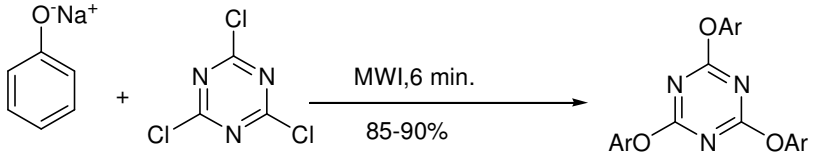
1. Reactions using neat reactants
2. Reactions using solid-liquid phase transfer catalysis (PTC)
3. Reactions using solid mineral supports.

For carrying out reactions with neat reactants i.e without the use of a solvent or a support (Heterogeneous reactions), at least one of the reactants at the reaction temperature should normally be liquid. In such a set-up, either the solid is partially soluble in the liquid phase or the liquid is adsorbed onto the surface of solid with the reaction occurring at the interface. There is also another possibility, namely that both the reactants are solid. Usually, they melt during the reaction course and then undergo reaction as described above[57].

Following are the Examples of Microwaves assisted Reactions with neat reactants-

1. **Aromatic Nucleophilic Substitutions**

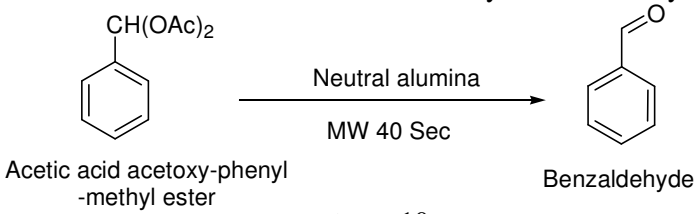
Formations of Substituted Triazines[58,59]Aromatic nucleophilic substitutions are carried out using sodium phenoxide and 1, 3, 5-trichlorotriazine under microwave irradiation (6 min). The products, 1, 3, 5-triarlyoxytriazines are obtained in 85–90% yields.



Scheme-9

2. Deacetylation[60]

Aldehydes, phenol and alcohols are protected by acetylation. After the reaction, the deacetylation of the product is carried out usually under acidic or basic conditions the process takes long time and the yields are low. Use of microwave irradiation reduces the time of deacetylation and the yields are good.



Scheme-10

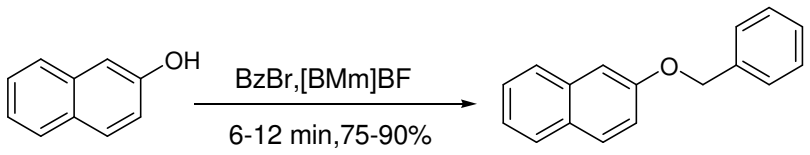
Microwave assisted Reactions using phase transfer catalysis (PTC)

Solid liquid phase transfer catalysis (PTC) has been described as an effective method in organic synthesis and is under active investigation. This method is specific for anionic reactions as it involves anionic activation. A catalytic amount of a tetralkylammonium salt or a cat ion complexing agent is added to the mixture (in equimolar amounts) of both pure reactants. Reactions occur in the liquid organic phase, which consists here only of the electrophilic R-X. The presence of an additional liquid component is disadvantageous as it induces a dilution of reactants and consequently a decrease in reactivity. The electrophile R-X is therefore both the reactant and the organic phase for the reaction.

Following are the Example of Microwave assisted Reaction using Solid Liquid Phase-

1. O-Alkylation

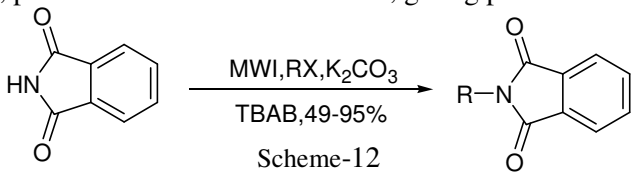
Preparations of ethers were carried out from β-naphthol using benzyl bromide and 1-butyl-3-methyl-imidazolium tetrafluoroborate under microwave irradiation (6-12 min) the products were isolated in 75-90% yields.



Scheme-11

2. N-Alkylations[61] [63]

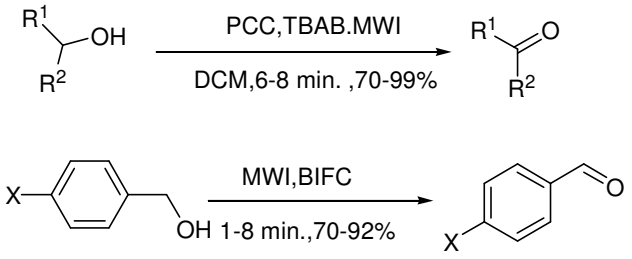
N-Alkylations under microwave irradiation using phase transfer catalysts occupy a unique place in organic chemistry. Bogdal and co-workers reported the synthesis of *N*-alkyl phthalimides using phthalimide, alkyl halides, potassium carbonate and TBAB; giving products in 45–98% yields.



Scheme-12

3. Oxidations[62]

Chakraborty reported the oxidation of secondary alcohol and benzyl alcohols using phase transfer catalysts. Oxidation of secondary alcohols to acetone derivatives was carried out using PCC, tetrabutylammonium bromide and dichloromethane under microwave irradiation (6–8min), products were isolated in 70–99% yields. Oxidation of benzyl alcohols was conducted using BIFC under microwave irradiation (1–8 min) yielding benzaldehyde derivatives in 70–92% yields.



Scheme-13

Digestion

Development of high pressure Asher focused microwave (HPAFM) a novel approach to microwave digestion is described by H. Matusiewics[63].The system uses focused MW operating at 2.45 GHz at 650 W power. The pressure vessels are made up of quartz discover pressure and temperature can be conducted up to 130 bars and 320_ C respectively. Using this apparatus the methodology was developed for digestion of biological reference material such as bovine liver.

Microwave irradiation in waste management

Microwave heating is plying an important role in treatment of domestic and hazardous industrial and nuclear waste. Microwave heating can be advantageously used for waste management in areas where human exposure can cause health problems. The MW and high frequency technology needed for handling such type of hazardous waste is ready to use.

A process for carbonization of organic waste for manufacturing of activated carbon using MW heating has been patented by Kasai et al.[64]Activated carbon can be manufactured form organic wastes such as used paper, wood, waste plastic etc. in high carbonization efficiency using MW heating. The method and apparatus for continuous and batch process is developed for waste treatment by Roszel[65].In this process waste such as automobile shedder waste, medical wastes, ores, sludge etc are treated by MW energy in anaerobic atmosphere.

Advantage of Microwaves

i. Rapid reactions
ii. High purity of products
iii. Less side-products.
iv. Improved yields.
v. Simplified and improved synthetic procedure.
vi. Wider usable range of temperature.
vii. Higher energy efficiency.
viii. Sophisticated measurement and safety technology.
ix. Modular systems enable changing from mg to kg scale.

Disadvantages of Microwaves

i. Heat force control is difficult
ii. Water evaporation.
iii. Closed container is dangerous because it could be burst.

CONCLUSION

Microwave is a convenient way toward the goal of green/sustainable chemistry, and is strongly recommended to use in organic preparations of Pharmaceutical chemistry.

The examples cited above are impressive and provide a good insight into the field of microwave assisted organic synthesis. The benefits of microwave-assisted organic synthesis are increasingly making the technique more established worldwide. In order to achieve further development in this field, novel instruments, which give rise to reproducible performances and that constitute a minimal hazard should be used instead of the domestic microwave ovens.

REFERENCES

1. F.Mavandadi and A.Pilotti, *Drug Discovery Today*, **11(3-4)**, 165 (2006).
2. C.A.Tsoleridis, C.G.Neochoritis, T.Tzitzikas, J.Stephanatou, C.A.Kontogiorgis, D.J.Hadjipavlou-Litina, and T.Choli-Papadopoulou, *European Journal of Medicinal Chemistry*, **46(1)**, 297 (2011).
3. F.Langa, P.De la Cruz, A.De la Hoz, A.Díaz-Ortiz and E.Díez-Barra, *Org. Synth*, **4**, 373 (1997).
4. C.R.Strauss and R.W.Trainor, *Aust. J. Chem*, **48(10),** 1665 (1995).
5. A.Díaz-Ortiz, P.Prieto and E.Vázquez, *Syn. Lett.*, 269 (1997).
6. P.Lidström, J.Tierney, B.Wathey and J.Westman, *Tetrahedron*, **57**, 9225 (2001).
7. C.O.Kappe, and A.Stadler, Microwaves in Organic and Medicinal Chemistry June **2005**, XII.410 pages, Hand cover.
8. B.Wathey, J.Tierney, P.Lidström, and J.Westman, Drug Discovery Today, **7(6)**, 373 (2002).
9. C.A.Tsoleridis, C.G.Neochoritis, T.Tzitzikas, J.Stephanidou-Stephanatou, C.A.Kontogiorgis, D.J.Hadjipavlou-Litina, and T.Choli-Papadopoulou, *European Journal of Medicinal Chemistry*, **46(1)**, 297 (2011).
10. D.Prasad, A.Preetam, and M.Nath, *Comptes Rendus Chimie*, **15(8)**, 675 (2012).
11. S.Wang, C.Cheng, F.Wu, B.Jiang, F.Shi, S.Tu, G.Li, *Tetrahedron*, **67(25)**, 4485 (2011).
12. J.L.Tucker, *Org Process Res Dev*, **14**, 328 (2010).
13. T.Erdmenger, C.Guerrero-Sanchez, J.Vitz, R.Hoogenboom, and U.S.Schubert, *Chem Soc Rev*, **39**, 3317 (2010).
14. V.Santagada, F.Frecentese, E.Perissutti, L.Favretto, and G.Caliendo, QSAR Comb Sci, **23**, 919 (2004).
15. C.O.Kappe, Angew Chem Int Ed, **43**, 6250 (2004).
16. R.K.Sekhon, M.W.Schilling, T.W.Phillips, M.M.Hasan, M.J.Aikens, R.Nannapaneni, and W.B.Mikel, *J. Food Science*, **75(5)**, 452 (2010).
17. V.Santagada, F.Frecentese, E.Perissutim, F.Fiorino, B.Severino, and G.Caliendo, Review. *Mini Rev Med Chem*, **9**, 340 (2009).

18. D.Bogdal, P.Penczek, J.Pielichowski, and A.Prociak, *Adv. Polym. Sci.*, **163**, 193 (2003).
19. J.D.Moseley, P.Lenden, A.D.Thomson, and J.P.Gilday*, Tetrahedron Lett*, **48**, 6084 (2007).
20. A.Hoz de la, A.Dfaz, A.Moreno, *Chem. Soc. Re*, **34**, 164 (2005)
21. (a.) R.N.Gedye, J.B.Wei, *Can. J. Chem*., **76**, 525(1998). (b.)R.S.Varma; *Green Chem*., **1**, 43(1999)
22. (a) D.M.P.Mingos, A.G.Whittaker; R.V.Van, C.Malik; D. Hubbard; John Wiley and Sons and Spektrum Akademischer Verlag Co- Publication, New York and Heidelberg, 1997, 479.(b) D.M.P.Mingos; D.R. Baghurst, H.M.Kingston, S.J. Hazel, A.C.S, Washington D. C., 1997, 455.
23. (a) M.Nuchter, B.Ondruschka, A.Jungnickel, U.Muller, *J Phys. Org. Chem.*,**13***,* 579 (2000). (b) M. Nuchter, B. Ondrushka, W Lautenschlager, *Synth. Commu,* **37***,* 1277 (2001).
24. J.W.Vanderhoff, *U. S. 3*, 1969, 432- 413, *Chem. Abstr.*, **70***,* 97422v, 1969.
25. R.Gedye, F.Smith, K.Westaway, H.Ali, L.Baldisera, L.Laberge, J.Rousell, *Tetrahedron Lett., **27**,* 279 (1986).
26. R.J.Giguere, T.L.Bray, S.M.Duncan, G.Majetic, *Tetrahedron Lett,* **27***,* 4945 *(*1986).
27. C.J.Li, *Chem. Rev.,* **93***,* 2023 (1993).
28. C.O.Kappe, D.Dallinger, *Nat. Rev. Drug Discovery, **5**,* 51 (2006).
29. V.Polshettiwar, R.S.Varma, *Acc. Chem. Res, **41**,* 629 (2008).
30. V.Polshettiwar, R.S.Varma, *Chem. Soc. Rev., **37**,* 1546 (2008).
31. S.A.Galema, B.S.J.Halstead, D.M.P.Mingos, *Chem. Soc. Rev*., ***2**,* 213 (1998).
32. R.Trotzki, M.Nuchter, B.Ondruschka, *Green Chem., **5**,* 285 (2003).
33. S.Horikoshi, T.Hamamura, M.Kajitani, M.Yoshizawa-Fujita, N.Serpone, *Org. Process Res. Dev*., ***12**,* 1089 (2008).
34. R.S.Varma, *Green Chem*., ***1**,* 43 (1999).
35. R.N.Gedye, F.E.Smith, K.C.Westaway, *Can. J. Chem., **66**,* 17 (1988).
36. H.M.Kingston, L.B.Jassie, A.C.S, Washington D. C., Ch. **2**, pp 110 (1988).
37. J.Andrews, G.F.Atkinson, *J. Chem. Edu., **61**,* 177 (1984).
38. R.Breslow, *Acc. Chem. Res, **24**,* 159 (1991).
39. P.A.Grieco, *Aldrichimica Acta, **24**,* 59 (1991), *Chem. Abstr.*, ***116***, 99425r (1992).
40. A.K.Bose, M.S.Manhas, B.K.Banik, E.W.Robb, *Res.Chem. Intermed, **20**,*1 (1994).
41. A.K.Bose, B.K.Banik, N.Lavlinskaia, M.S.Manhas, *Chem. Tech., **27**,* 18 (1997).
42. A.Lubineau, J.Auge, Y.Queneau, *Synthesis*, 741 (1994).
43. P.A.Grieco, E.B.Brandes, S.McCann, J.D.Clark, *J. Org.Chem., **54**,* 5849 (1989).
44. R.Laurent, A.Laporterie, J.Dubac, J.Balam, S.Lefeuvre, M.Audhuy, *J. Org. Chem*., ***57**,* 7099 (1992).
45. W.Blokzijl, J. B. F. N.Engberts, *Angew Chem., Int. Ed.*, ***32***, 1545 (1993).
46. M.Martelanc, K.Kranjc, S.Polanc, M.Koevar, *Green Chem., **7**,* 737 (2005).
47. E.M.Kirschner, *Chem. Eng. News, **72**,* 13 (1994).
48. D.L.Illman, *Chem. Eng. News, **72**,* 22 (1994).
49. M.A.Herrero, J. M.Kremsner; C. O.Kappe *J. Org. Chem., **73**,* 36 (2008).
50. J.Hren, K. Kranjc, S.Polanc, M.Koevar, *Synthesis,* 452 (2008).
51. R.N.Gedye, W.Rank,K.C.Westaway, *Can. J. Chem*, **69**,700 (1991).
52. M.N.Gedye, FE Smith, K.C.Westaway, *Can. J. Chem*, **66**, 17(1988).
53. R.N.Gedye, E.Smith, K.Westaway, H.Ali Baldisera, L.Laberge, J.Rousell, *Tetrahedron lett.,* **27**, 279 (1986).
54. G.B.Jones, B.J.Chapman, *J. Org Chem.*, **58**, 5558 (1993).
55. A.R.Katritzky, Y.Zhang, S.K.Singh, P.J.Steel, *Arkivoc,* **xv***,* 47 (2003).
56. (a)A.Vass, J.Dudas, R.S.Varma, *Tetrahedron Lett, **40**,* 4951 (1999).(b) L.Perreux, Loupy, F.Volatron, *Tetrahedron,* ***58***, 2155 (2002). (c) A.Loupy, D.Monteux, A.Petit, J.M.Azipurua, E.Dominguez, C. Palomo, *Tetrahedron Lett, **37**,* 8177 (1996). (d) A.R.Hajipour, S.E.Mallakpour, A.Afrousheh, *Tetrahedron, **55**,* 2311 (1999). (e) S.Frere, V.Thiery, T.Besson, *Tetrahedron Lett, **42**,* 2791 (2001). (f) J.A.Vega, J.J.Vaquero, J.Alvarez- Builla, J.Ezquerra, C.Handouchi, *Tetrahedron, **55**,* 2317 (1999). (g) A.Diaz-Ortiz, P.Prieto, A.Loupy, D.Abenhaim, *Tetrahedron Lett., **37**,* 1695 (1996). (h) C.Limousin, J.Cleophax, A.Loupy, A.Petit, *Tetrahedron, **54**,* 13567 (1998). (i) K.Bougrin, A.Loupy, A.Petit, B.

Daou, M.Soufiaoui, *Tetrahedron,* ***57,*** 163 (2001). (j) S.Paul, M.Gupta, R.Gupta, A.Loupy, *Tetrahedron Lett,* ***42,*** 3827 (2001). (k) K.G.Kabza, B.R.Chapados, J.E.Gestwicki, J.L.McGrath, *J. Org. Chem*., ***65,*** 1210 (2000).
57. A.Seijas, M. P.Vazquez-Tato, *Chimica Oggi,* ***25***, 20 (2007).
58. J.A.Seijas, M.P.Vazquez-Tato, M.M.Martinez, G.N.Corredoira, *J. Chem. Res.(S),* 420 (1999).
59. Z.Dahmani, M.Rahmouni, R.Brugidou, J.P.Bazureau, J.Hamelin, *Tetrahedron Lett.,* ***39,*** 8453 (1998).
60. D.Scharn, H.Wenschuh, U.Reineke, J.Schneider-Mergener, L. Germeroth, *J. Comb. Chem.,* ***2,*** 361 (2000).
61. D.Bogda, J. Pielichowski, A.Borona, *Synlett,* 873 (1996).
62. V.Chakraborty, M.Bordoloi, *J. Chem. Res. (S),* 118 (1999).
63. H.Matursievicz, *Anal Chem.*, **71(15)**, 3145 (1999).
64. T.Kasai, S.Abe, S.Kanbayashi, S.Okada.J.P, **34**,114, *Chem. Abstr.*, **132,124894h** (2000).
65. P.W.Roszel, US 20 26103, *Chem Abstr.*, **117,177752g**.

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