REVIEW ARTICLE

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MORE Chemistry: An Eco-friendly Technology

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Microwave-induced organic reaction enhancement chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis. Important features of this technique are easy access to very high temperature, good control over energy input in a reaction and rapid synthesis of organic compounds. The advantages of microwave-induced organic reaction enhancement chemistry include requirement of simple, inexpensive instrument, lesser quantities of solvents and eco-friendly technology. It can be termed as 'e-chemistry' because it is easy, effective, economic and eco-friendly and is believed to be a step towards green chemistry. In this review, we have discussed development of microwave-induced organic reaction enhancement chemistry, methods involved in reaction set up and it's pharmaceutical applications.

Microwave-induced organic reaction enhancement (MORE) chemistry is just more than a decade old concept used by many biochemists and chemists[1-6] for hydrolytic reactions and organic synthesis[7]. It is gaining popularity as a non-classical approach due to its utility in highly accelerated synthesis of divergent types of organic compounds. Traditionally, commercial microwave ovens are used as a convenient source of energy in chemical laboratories for efficient heating of water[7], moisture analysis[5] and wet ashing procedures of biological and geological materials[8-14]. Their computerized versions are commercially available for acid digestion of ores and minerals in explosion proof vessels and for rapid determination of thermodynamic function of chemical reactions[8]. Application of microwave technology to catalytic hydrogenesis of alkenes, hydrocracking of bitumen obtained from tar sand, degradation of polychlorinated hydrocarbons[15], waste material management, polymer and ceramic technology are well known. In 1986, Gedye *et al.*[5] and Giguere *et al.*[4] demonstrated that many organic reactions can be conducted very rapidly under microwave irradiation[16]. Since the appearance of these two pioneering reports and the first review appearing in 1989, many researchers have described 'accelerated organic reactions' and number of papers have appeared proving the utility of MORE chemistry in routine organic synthesis[17]. Short response time and highly accelerated reaction rate are main advantages of MORE chemistry. In this review, we have tried to highlight the design of a MORE reaction and its applications in the synthesis of organic molecules, which may be useful in the development of various compounds having pharmaceutical applications.

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The microwave equipment:

In the past few years, microwave heating has been found to be a convenient source of energy not only in the kitchen but also in chemical laboratories. Microwaves form a part of electromagnetic radiations with a wavelength lying between 1 cm and 1 m. A commercial microwave oven with automatic power settings, starting at 72 watts and increasing up to 720 or 1200 watts is a suitable instrument. It provides a narrow beam of microwaves generated by a magnetron set at a frequency of about 2450 MHz (λ 12.25 cm)[18]. Main difference between microwave energy and other forms of radia-

tion like X-rays is that microwave energy is non-ionizing and therefore, does not alter molecular structure. It provides only thermal activation[16]. The domestic microwave oven can be directly used in MORE chemistry without any modification. Sometimes, specially modified instruments may be employed for the purpose[19]. But, modification of commercial equipment can be hazardous due to possible leakage of microwave radiations. The main precaution in using a microwave oven is that no metallic object (such as a spatula) should be exposed to microwave radiations because it causes arcing[16]. Multimode domestic microwave ovens are well suited for any robust organic reaction, provided adequate safety precautions are taken. However, use of microwave reactors designed for organic reactions is highly recommended.

Reaction methods and vessels:

Reaction mixture is 'zapped' under microwave irradiation in a reaction container made of Teflon, polystyrene or glass[7]. These materials are nearly transparent to microwaves. They absorb the radiation poorly and can withstand high temperature generated in reaction mixture[16]. Reactions can be carried out using any one of the following methods and apparatus.

Sealed Teflon bomb:

Sealed vessels are commonly employed as reaction containers to conduct reaction up to a few grams scale[4]. Teflon is widely used material for preparation of sealed containers[5], which are commonly referred to as 'Teflon bomb'. In sealed vessels, very high temperature and high pressure are rapidly attained. This leads to a remarkable increase in rate of reaction resulting in dramatic time saving. But, this high pressure also increases the risk of explosion during microwave irradiation, which is the main limitation to the use of sealed reaction containers. Giguere *et al.*[4] designed an explosion proof device in which a sealed reaction vessel made of Teflon or glass is covered with vermiculite that serves to absorb the reaction content in the event of explosion. It is then placed in either a Corian box, Nalgene desiccator or a container made of a special polymer, which has the ability to withstand high temperature and pressure. When Teflon is used, microwave exposure of more than 15 min should be avoided as it softens the material, resulting in the risk of loss of reaction content.

Several reactions are reported to occur at a rapid rate in sealed vessels. To mention a few, the esterification of benzoic acid with methanol proceeds almost 100 times faster in a microwave oven as under reflux, while the synthesis of 4-cyanophenyl ether (SN_2 reaction) is accomplished with a rate enhancement of about 240 times. It is observed that reaction rate is directly proportional to the pressure developed in the reaction vessel. A thousand fold rate enhancement is reported when the SN_2 reaction is carried out in a 50 ml Teflon bomb against a 240-fold increase in a 250 ml vessel[5].

DRY MEDIA SYNTHESIS

Main disadvantage to the use of a sealed tube or Teflon bomb is the danger of explosion due to high pressure generated during microwave irradiation. This high pressure can be avoided by conducting the reaction in 'neat condition' or by using inorganic solid support.

Neat reaction[4,20,21]:

It is a reaction carried out without using any solvent or catalyst. A mixture of only reactants without solvent helps to avoid the risk of high pressure in a sealed vessel. Certain reports indicate that MORE reaction in neat condition produce products in better yields than classical methods. For example, Tandem ene/intramolecular Diel's Alder reaction[22] resulted in 82% yield with 6 min microwave exposure as against 40% yield obtained upon 20 h reflux[23]. However, the utility of neat reactions in routine organic synthesis is limited.

Solid phase reaction using inorganic support[16,24-26]:

In recent years, it has been proved that several inorganic solids can be useful as catalysts in organic reactions. A reaction can be carried out by adsorbing the reactants on an inorganic solid support in a sealed or open vessel under microwave environment. Clay, silica, bentonite, alumina and zeolite are widely used support[16,27-29]. Microwaves are absorbed only by the reactants adsorbed on the surface of inorganic oxides; therefore, numerous reactants supported on a solid surface can be effectively used to conduct organic reactions under very safe and simple conditions[25,30,31,33]. Moreover, these solids prevent development of high pressure in sealed containers. Practical feasibility of microwave assisted solvent free protocols has been demonstrated in useful chemical transformations like protection, deprotection, oxidation, reduction and condensation reactions. Many reports have appeared in recent years showing the use of solid support in heterocyclic compound synthesis[24,25,31,35]. For instance, synthesis of 3-methyl-6-[2-chloro-2-(4-chlorophenyl) ethenyl]-5,6-dihydro-s-triazolo-(3,4-b)(1,3,4)-thiadiazole was obtained in 79% yield in a microwave oven on 16 min exposure using acidic alumina support while only 69% yield was

reported in the classical method involving 12 h heating[7].

Open vessel reaction using solvents[5-14]:

MORE reaction can be carried out by using simple, inexpensive and safe equipment like an open Borosil beaker, conical flask or Erlenmeyer flask[33]. A simple reaction vessel is a tall beaker with a loose cover having much larger capacity than the volume of the reaction mixture. An Erlenmeyer flask with funnel cover can also be used and a watch glass may be placed over funnel to avoid excessive solvent evaporation during microwave heating[16]. Recent modification involves carrying out the reaction in a flask fitted with condenser that is charged with cold non-polar solvent like xylene or carbon tetrachloride. This has increased the utility of the domestic microwave oven in organic synthesis[17,37]. As commercial ovens are equipped with fans to remove hot air and vapors from inside the oven, no safety hazard is commonly experienced when the solvent is overheated in an

TABLE 1: COMMONLY USED ENERGY TRANSFER MEDIA IN 'MORE' CHEMISTRY.

Energy Transfer Medium	Boilling Point	Dielectric Constant (At 20/25°, unless specified)[a]
Acetone	56.5	20.70
Acetyl acetone	140.6	25.70
Acetonitrile	82.0	37.50
Benzene	80.1	2.27
1-Butanol	117.7	17.80
Carbon disulfide	46.3	2.64
Carbon tetrachloride	76.7	2.23
Chlorobenzene	132.1	5.62
Chloroform	61.7	4.81
1,2-Dichloroethane	83.5	10.65
Diethyl ether	34.6	4.34
Diethylene glycol	244.8	31.70
Dimethyl formamide	153.0	36.71
Dimethyl sulfoxide	189.0	46.60
1,4-Dioxan	101.1	2.21
Ethanol	78.4	32.40
Ethyl acetate	77.1	6.02
Ethylene glycol	124.0	38.66
n-Hexane	68.7	1.89
1-Hexanol	157.5	13.30
Methanol	64.7	32.70
Pyridine	115.5	12.30
Tetrahydrofuran	66.0	7.58
Toluene	110.6	2.38
Water	100.0	78.50
m-Xylene	139.1	2.37
p-Xylene	137.8	4.80 (At 61.2°)

a: Dielectric constant are temperature dependant. Unfortunately, data regarding this at high temperatures are rare or non-existent.

open vessel[25,38,39].

Energy transfer medium:

In MORE technique, organic solvents serve as an energy transfer medium. High boiling solvents like N,N-dimethyl formamide (DMF), o-dichlorobenzene, 1,2-dichloroethane (DEC) are used commonly[4,5,38]. Polar solvents with a high dielectric constant absorb microwave energy better than non-polar solvents due to dipole rotation and are, therefore, heated rapidly with higher energy transfer rates[3]. Thus, DMF and DEC are heated much faster than hexane or carbon tetrachloride in a microwave oven. Superheating of liquids is common under microwave irradiation. Water, for example, reaches 105° (5° above actual boiling point) and acetonitrile reaches 120°, an amazing 38° higher than its boiling point[16,39]. This superheating, which is not commonly seen in conventional heating, may help in increasing the rate of reaction. Rate of temperature increase is not only a function of dielectric properties but also the ionic strength, specific heat capacity, emmissivity, geometry, sample volume and strength of the applied field[40]. In practice, and as a general rule, almost all types of organic reactions that require heat can be performed using microwaves.

DMF is an excellent energy transfer medium for many types of organic reactions carried out under microwave environment. It is a good solvent with high boiling point (153°) and dielectric constant (ε=36.7). It can retain water formed in a reaction, thus eliminating the need of water seperator[3,7]. Reaction temperature rapidly rises to about 140° in an open container without any significant evaporation of solvent, while temperatures exceeding 300° are attained in sealed tubes with microwave heating. Boiling point and dielectric constant of commonly used solvents are listed in Table 1, parameters considered for solvent selection in MORE chemistry[41-43].

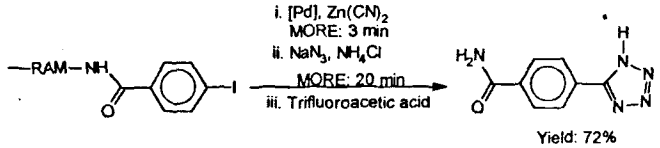
Fast reaction monitoring:

A rapid method for fast monitoring of MORE reactions was reported by Bose *et al.*[7] It consists of thin layer chromatography followed by chemical ionization mass spectroscopy (TLC-CIMS). The spot on a TLC plate, after isolation, is transferred rapidly to a mass spectrometer. Molecular weight and fragmentation pattern generally permits quick identification of products of a reaction. For additional data, the spot from TLC plate can be eluted and analyzed by IR and NMR studies. Fast monitoring by TLC-CIMS adds to the overall efficiency of synthetic experiments conducted in a microwave oven.

APPLICATIONS

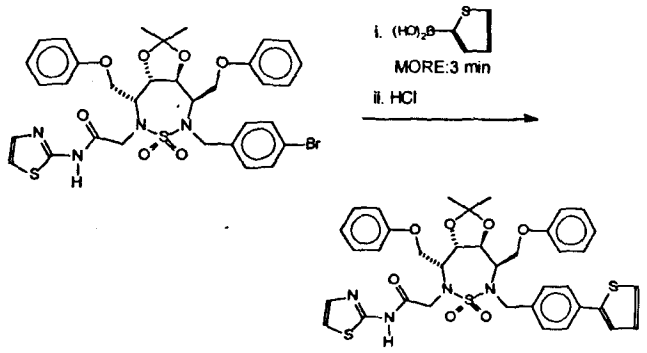
Rapid synthesis of drug molecules:

MORE chemistry has been used in the synthesis of organic drugs with varied biological activities, which is evident from available reports. For example, triazolo-thiazoles (cyclic analogues of thiasemicarbazides[44] and biguanides[45] having different biological actions)[25,39,46], α-vinyl-β-lactams (synthetic β-lactams)[16], 3,4-dihydro isoquinoline[16], 4-aryl-1,4-dihydro pyridine (calcium channel blockers)[17] have been effectively synthesized in good yields and purity by MORE technique (Table 2). Tetrazoles are of particular interest to medicinal chemists because they constitute probably the most widely used bioisostere of the carboxyl group. MORE technique has been found suitable for the synthesis of tetrazoles of biological interests from iodides via nitriles[47] (Scheme 1). Similarly, the Suzuki reaction used in the preparation of a cyclic inhibitor of HIV-1 protease in good yields[48] is depicted in Scheme 2. Utility of MORE chemistry in fast synthesis of sildenafil (Viagra™) in quantitative yields is shown in Scheme 3.



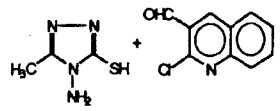
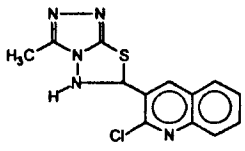
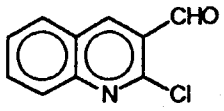
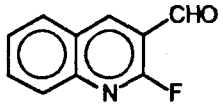
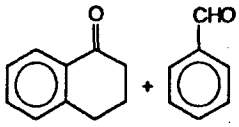
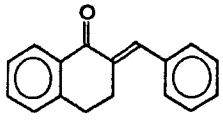
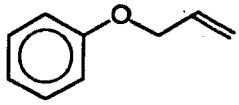
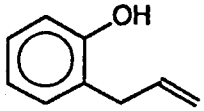
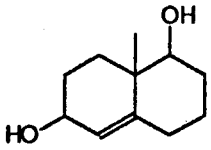
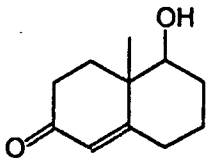
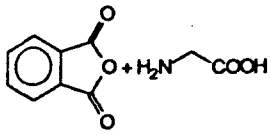
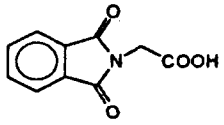
-RAM: Rink resin amide

Scheme 1: Synthesis of aryl tetrazoles from iodides.



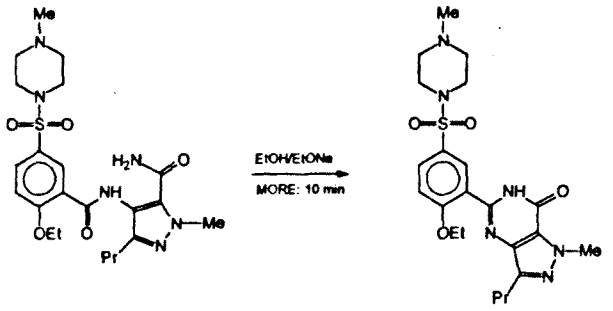
Scheme 2: Synthesis of non-symmetric cyclic sulfonamide HIV-I protease inhibitor by Suzuki coupling.

TABLE 2: REACTION TIME AND YIELDS OF IMPORTANT REPORTED REACTIONS.

Examble (reaction method)	Reactants	Products	Reaction Time		Yield (%)		Ref
			MORE (min)	Classical (h)	MORE	Classical	
Cyclization, synthesis of triazolo thiadiazolyl quinoline (On Alumina support)			17	14	83	73	7
Aromatic fluorination (Acetamide solvent)			02	4.5	94	82	51
Synthesis of chalcones (Ethanol solvent)			16	64	56	50	60
Ortho-Claisen condensation (DMF solvent)			05	36	97	72	62
Oxidation reaction (Diethyl ether solvent)			07	1.5	93	36	62
Phthaloylation of amino acids (On silica gel support)			03	04	100	95	69

Synthesis of drug intermediates/synthon:

It is well known that fluorine in organic compounds leads to increase in lipid solubility[50]. MORE chemistry is useful in replacement of chlorine in aromatic systems by fluorine rapidly[51]. Some of the common reactions like oxidation and molecular rearrangement reactions used in classical organic synthesis are given in Table 2. Several intermediates useful in heterocyclic drug synthesis such as 3-formyl indole are reported to be synthesized rapidly[49,53]. Similarly, substituted imidazoles are important intermediates for development of biologically active compounds, which can be obtained in higher yields by MORE technique[71] (Scheme 4). Chiral syn-

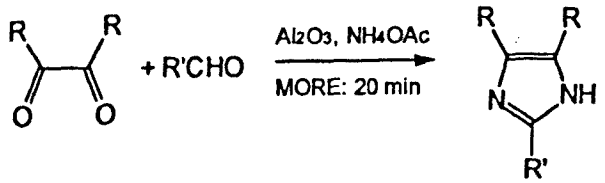


Scheme 3: Microwave-assisted cyclization and dehydration reaction used in the synthesis of sildenafil (Viagra™).

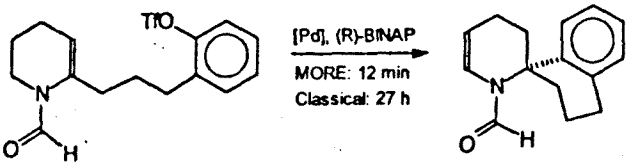
thesis is an important area that is also benefited by this technology. An example illustrating asymmetric Heck synthesis[63] is given in Scheme 5.

Laboratory experiments:

A substantial amount of savings in time and reagents can be achieved by applying MORE methodologies in the routine organic chemistry experiments at undergraduate and post-graduate levels. It is proved to be fast, safe and economic at the university laboratories. Chemistry students can perform time consuming experiments like preparation of N-phthaloyl glycine, fluorescein and phenolphthalein in the limited time available (90-120 min)[16].



Scheme 4: Diverse substituted imidazoles obtained under solvent free protocols.



Tf. Triflate, BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

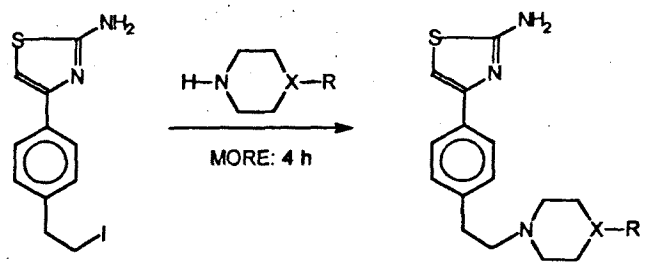
Scheme 5: Microwave-induced enantioselective Heck reaction.

Combinatorial chemistry:

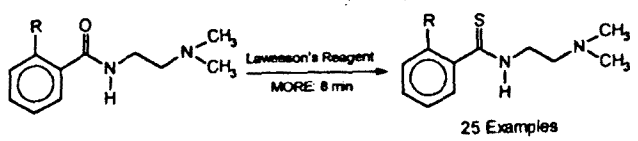
Combinatorial chemistry and multiple parallel synthesis involve synthesis of a large number of related chemicals (library)[54-56]. Development of high throughput screening methods has made it possible to determine thousands of data points weekly[57]. The demand of new compounds for such screening is increasing. The rate of lead optimization is often limited by the speed of orthodox organic synthesis. Any methodology that enables an acceleration of analogue synthesis will have an important role in drug discovery. Hence, MORE chemistry can benefit development of combinatorial methods, by which thousands of non-peptide molecules could be prepared simultaneously. For instance, Selway and Terrett[58] used microwave heating to achieve quick and convenient alkylation of 60 piperidines and piperazines to generate a library by parallel synthesis (Scheme 6). This library was screened in Herpes Simplex Virus-1 (HSV-1) helicase ATPase assay and confirmed hits were identified. Another example of rapid thioamide library[75] generation is given in Scheme 7.

Large scale manufacture of fine chemicals/drugs:

This technique is yet to prove its utility in bulk manufacture of chemicals and drugs in India. It can be used effectively in industry, which will reduce the time, labor and cost of drug synthesis and be commercially viable.



Scheme 6: Microwave promoted nucleophilic substitution used to produce a library of 48 antiherpes aminothiazole derivatives.



Scheme 7: Parallel transformation of a library of amides into the corresponding thioamides.

Advantages:

MORE chemistry offers a simple, non-conventional technique for the synthesis of a wide variety of compounds having medicinal, pharmaceutical and commercial importance. Highly accelerated reaction rate is the main advantage, which enables chemists to carry out a synthesis in much lesser time and reasonably good yields. It provides a rapid and inexpensive access to very high temperature and pressure in sealed containers like Teflon bomb. Currently available classical methods require elaborate apparatus, longer heating times, large volume of organic solvents and it allows virtually no control over energy input. Recent simplifications of MORE technique have increased safety and practical utility of the microwave oven for their use in organic laboratories without any modification. Furthermore, there is no need of sealed vessels, reflux condensers, stirrers, water separators (Dean-Stark tube) for routine synthesis. Solvents used in organic synthesis are of major concern as environmental pollutants, many of which are proved carcinogenic, mutagenic and allergens. An eco-friendly method is an important salient feature of MORE chemistry, since it requires no solvent (dry media synthesis) or very little solvent as energy transfer medium. Rapid synthesis also results in lesser evaporation of solvents preventing environmental pollution.

CONCLUSIONS

MORE chemistry has been identified as current trend in organic synthesis and initial doubts about MORE chemistry- a myth or reality no longer holds[59]. Entry of microwave oven in chemistry laboratory has made it possible to carry out many organic transformations with great efficiency and ease of work up. We hope that appropriate technology can be developed so that MORE chemistry is used for industrial manufacture of fine chemicals, thereby improving overall process, cost effectiveness and reducing pollution of the environment through the use of solvent free protocols.

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