Journal of Scientific & Industrial Research
Vol. 63, August 2004, pp 641-654

Microwave–assisted combinatorial chemistry: The potential approach for acceleration of drug discovery

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Received 21 January 2004; accepted 05 May 2004

In the present scenario, pharmaceutical companies are under pressure to speed-up their drug discovery programmes and to lower the cost of discovering new medicines. Combinatorial chemistry and high through put synthesis are almost well established as potential means of speeding up the drug discovery process, these techniques have been embraced widely by the pharmaceutical industry but there is still more need to speed-up the drug discovery. The use of microwave energy to combinatorial synthesis is one potential way to accelerate drug discovery. The advantages of microwave heating technology to combinatorial chemistry mainly includes dramatically reduced reaction time, increase in purity of resulting products and enhancement of chemical yields. In this review we discuss basic introduction to microwave theory which will enable researchers to understand at a molecular level the fundamental nature of phenomenon which results in heating and covered literature published which reveals advantageous nature of microwaves to combinatorial chemistry.

Keywords: Drug, Microwaves, Combinatorial chemistry, Drug delivery
IPC Code: **Int. Cl.**[7] : G 01 N 21/19

1 Introduction

High-speed combinatorial synthesis of peptides and small organic molecules using solid phase chemistry has emerged as a powerful tool for producing large chemical libraries for biological screening and drug discovery compared to traditional drug discovery approach which requires many days of work to synthesize and analyze a single new compound. Combinatorial chemistry can produce and screen one million compounds over a period of weeks for the discovery of novel drug entities against various disease targets. Faced with the increasing demand for novel drug targets, there is considerable current interest to accelerate the technologies associated with combinatorial chemistry and high throughput synthesis[1]. Since speed is generally recognized as an important factor in high-throughput synthesis and combinatorial chemistry, any technique that is able to accelerate the process of solid phase organic synthesis is of considerable interest. Recently, concept of speeding up resin-bound chemistry by microwave activation, i.e., MICROCOS technology (Microwave-assisted Combinatorial Synthesis) is creating lot of interest, both in academic and industrial communities[2]. The rapid heating of foodstuff in microwave oven is routinely used by a significant portion of mankind since 1970s the first report[3,4] about application of microwave energy for acceleration of organic reaction was published in 1986. The risk associated with flammability of organic solvents and the lack of available systems for temperature control were major concerns. Now safe microwave heating equipment are in market with devices for accurate temperature and pressure control and monitoring of reactions. As a consequence, lot of work has been done on MICROCOS technology (Figure1).

2 Basic Principles

In the electromagnetic spectrum the microwave radiation region is located between IR radiation and radio wave. Microwaves have frequencies between 0.3 and 300 GHz, corresponding to wavelengths between 1 mm and 1m, respectively. In order to avoid interference[5] with radar and telecommunication activities which operate within this region, most domestic and commercial microwave instruments operate at 2.45 GHz.

Heating occurs by two major mechanisms: (i) Dipolar polarization and (ii) Conduction.

2.1 Dipolar Polarization Mechanisms

For a substance to generate heat when irradiated

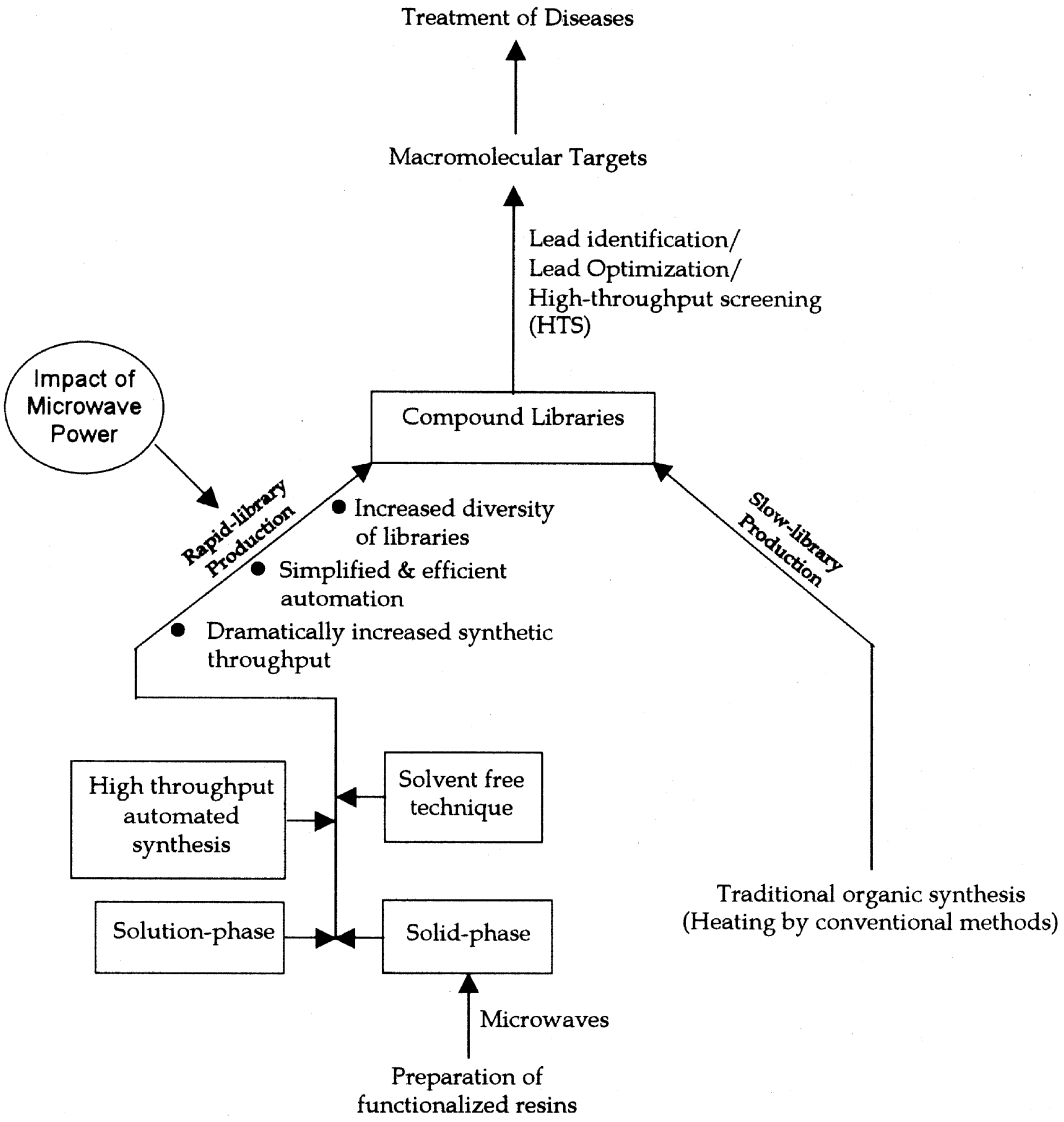


Fig. 1 — Impact of microwave power on acceleration of drug discovery. Microwave-assisted combinational chemistry has power to accelerate the generation of new drug molecules

with microwaves it must posses a dipole moment. It is the electric field component of the microwave irradiation, rather than magnetic field component, that is responsible for the effect, when a dipole tries to re-orientate itself with respect to an alternating electric field, it loses energy in the form of heat, by molecular friction. The heat generation is dependent on the nature of the dipole and the frequency of the applied radiation. If the frequency of the radiation is too high the dipole does not have time to align itself with the field before the field changes direction again. In these circumstances, no motion and consequently no heating occurs. Similarly, no heating occurs if the dipole aligns itself perfectly with the alternating electric field and, therefore, follows the field fluctuations[6]. However, if the applied field is in the intermediate frequency region (e.g. microwave radiation), a phenomenon occurs that lies between these two extremes. In this situation the dipole has time to respond and align itself with the field, but the fluctuations of the field are so rapid that the dipole does not follow it perfectly, this results in the generation of heat[7].

2.2 Conduction Mechanism

A solution containing ions or even a single isolated ion with a hydrogen bonded cluster, in the sample the ion will move through the solution under the influence of an electric field, resulting in expenditure

of energy due to an increased collision rate, converting the kinetic energy to heat[6].

2.3 Loss Angle

The ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature is calculated using the following equation: $\tan \delta = \epsilon''/\epsilon'$, where ϵ' is the relative permittivity, which is a measure of the ability of a molecule (or assembly of molecules) to be polarized by an electric field and ϵ'' is the dielectric loss, which is indicative of the ability of a medium to convert dielectric energy into heat. $\tan \delta$ is the dielectric loss tangent and defines the ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature. The value of $\tan \delta$ of an assembly of molecules depends on several factors which are as follows: (i) The frequency of the electromagnetic waves, (ii) The temperature, and (iii) The physical state and composition of the mixture. A high value for $\tan \delta$ indicates a high susceptibility to microwave energy (Table 1). Polar solvents have high $\tan \delta$ value and are, therefore, preferable for microwave-promoted reactions[8].

The relationship between $\tan \delta$ and ϵ' and ϵ'' is purely mathematical and can be described using simple trigonometric rules (Figure 2).

2.4 Superheating Effect

Using microwave heating, boiling points of solvents can be raised up to 26°C, above their conventional values, this phenomenon is known as superheating effect. This higher boiling point can be maintained in pure solvents for as long as the microwave radiation is applied.[9] However, substrates or ion that are present in solvent will aid the formation of 'boiling nucleuses'. In these situations the temperature will return to that of the normal boiling point of the solvent at a solvent dependent rate[10].

2.5 Solvents

It is well known fact that non-polar solvents are not heated under microwave irradiation. Ionic liquids absorb microwave irradiation in a very efficient manner and, additionally, they exhibit a very low vapour pressure, thereby enhancing their suitability even further for microwave heating.[6]

When the dielectric properties of the sample are too poor to allow efficient heating by microwave radiation the addition of small amounts of additives (ex-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 non-polar solvents for running syntheses using microwave radiation. 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, stable up to 200°C and have a negligible vapour pressure[11].

Table 1 — Dielectric constants and loss tangent values for some solvents relevant to organic synthesis

Solvent	Dielectric constant (ϵ_s)[a]	Loss tangent ($\tan \delta$)
Benzene	2.3	—
Carbon tetrachloride	2.2	—
Chloroform	4.8	—
Acetic acid	6.1	0.174
Tetrahydro furan	7.6	0.047
Methylene chloride	9.1	0.042
Methanol	32.7	0.659
Dimethyl forfamide	36.7	0.161
Dimethyl sulfoxide	47.0	0.825
Ethanol	24.6	0.941
Formic acid	58.0	0.722
Water	80.4	0.123

[a]The dielectric constant, ϵ_s equals the relative permitivity i.e. ϵ' at room temperature under the influence of a static electric field

[b] Values determined at 2.45Ghz and room temperature

2.6 Vessels

The reaction vessels are made of material that is virtually transparent to microwaves at the operating frequency. Borosilicate glass or poly tetrafluoroethylene (Teflon, which is resistant to strong bases and hydrogen fluoride) are most commonly used. However, if reactions are to be carried out under pressure in sealed systems the major concern is the ability of the vessel to withstand the changes in pressure and temperature associated with the particular transformation. The technology of vessel design is improving and a range of vessels are now available for carrying out reactions under pressure[5].

3 Microwave Equipment

Modes

When microwaves enter a cavity, they are reflected by the walls. The reflections of the waves eventually generate 3-*D* stationary pattern of standing waves within the cavity, called modes[6]. In a microwave oven radiation is generated by a magnetron the microwaves

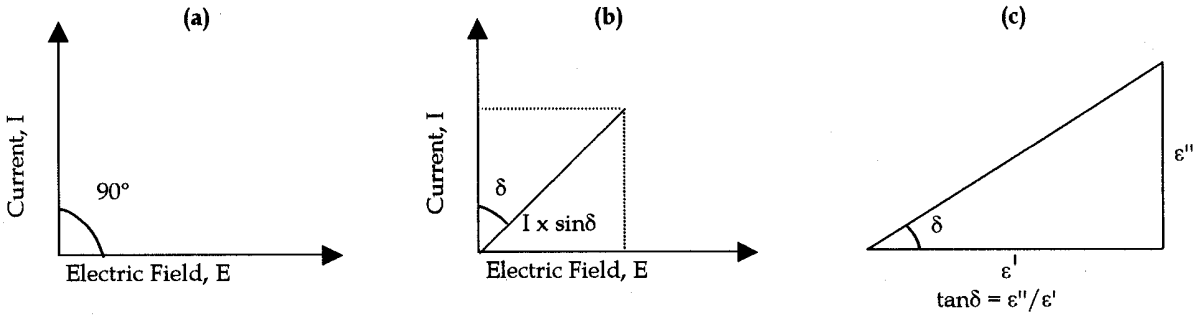


Fig. 2 — Phase diagrams for: (a) an ideal dielectric where energy is transmitted without loss, (b) phase displacement which results when energy is converted to heat, (c) the relationship between ε′ and ε″, tan δ = ε″/ε′

are guided into the cavity by a wave-guide and reflected by the walls of cavity. If the microwaves are not absorbed, they may be reflected back down the wave-guide and damage the magnetron. Thus, it is essential to have a microwave active "dummy load", which absorbs excess microwaves and avoid such damage[5].

To date the majority of microwave-promoted organic syntheses have been performed in multi-mode domestic ovens. In these ovens the power levels commonly fluctuate as a result of the pattern of switching of on-off cycles.[12,13] Multimode oven have several drawbacks: (i) The microwaves are heterogeneously distributed within the cavity and consequently less-defined regions of high and low energy intensity are produced, (ii) The temperature cannot be simply and accurately measured, (iii) The power is not tunable and is fact the sample is always subjected to maximum power levels for varying periods of time, and (iv) The reproducibility of experiments is poor, especially with small amounts of products.

These drawbacks led to the development of monomode microwave oven which focuses the electromagnetic waves in an accurately dimensioned wave-guide. They allow a homogeneous distribution of the electric field and can be used with a low entitled power with a high energetic yield[14]. Monomode reactors offer increased efficiencies and reliabilities. They lead to considerable improvements in yields of organic synthesis by preserving thermal stabilities of products with real low emitted power and good homogeneity in temperature[15].

Most of today's commercially available microwave reactors feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fiber-optic probes, shielded thermocouples or IR sensors, and software that enables on-line temperature pressure control by regulation of microwave power output. In single-mode cavities, only one mode is present and the electromagnetic irradiation is focused directly through an accurately designed wave-guide onto the reaction vessels mounted at a fixed distance from the radiation source. One drawback of single-mode cavities is that reaction size is more or less fixed at a relatively small volume. From combinatorial chemistry applications the key difference between the two types of reactor systems is that in multimode microwave oven several reaction vessels can be irradiated simultaneously in multi vessel rotors (parallel synthesis), whereas in monomode microwave oven, only one vessel can be irradiated at a time. In the latter case, high throughput can be achieved by integrated robotics that more individual reaction vessels in and out of the microwave cavity[16].

4 Microwave Assisted Combinatorial Synthesis Techniques

4.1 Solvent Free Technique

While performing microwave assisted syntheses in domestic microwave ovens, lack of control has lead to numerous explosions. One approach to avoid this problem is to omit the solvent from the reaction and perform the reactions on solid supports such as, various clays, aluminum oxides, and silica. This technique has been used for some interesting syntheses[14]. Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient, and economical technology, safety is largely increased, workup is considerably simplified, cost is reduced, increased amounts of reactants can be used in the same equipment. One limitation of using solvent free technique is that it is difficult to obtain good temperature control at the surface of the solids. This leads to problems regarding reaction

predictability, reproducibility, and controllability.

In 'solvent free' or 'dry-media' synthesis, a solid support capable of absorbing microwave radiation (such as, clay or alumina) is first impregnated with a solution of reactants in a volatile solvent. The solvent is removed by evaporation, and solid support with adsorbed reagents is irradiated by microwaves. In some cases, a small amount of *N*, *N′* – dimethylformamide (DMF) is added to the reaction as an energy transfer medium. The reaction takes place in the solid phase, and the products are then extracted from the support, using an appropriate solvent.

4.2 Pressurized Systems

Reactions performed under pressure in a microwave cavity benefit from rapid heating rates and remote heating of microwave dielectric heating. Most apparatus are now equipped with reliable temperature monitoring, temperature-feedback control, and pressure measurement devices that eliminate failures due to thermal runaway reactions and poor heating[13].

4.3 Reflux Systems

Now reflux systems are available which are either modified domestic oven or designed with single mode cavities, which can be used for microwave assisted organic synthesis without the risk of explosion due to the presence of organic solvent. However, there is little risk of explosions with these reflux systems since systems are at atmospheric pressure and flammable vapours cannot be released in to the microwave cavity.

4.4 Continuous Flow System

High power microwave equipments are large and not easy to accommodate, they often require water cooling when working with volume more than 500 mL. In this case multimode oven are used. An alternative approach is to use continuous flow system in which the reagents are pumped through the microwave cavity, allowing only a portion of the sample to be irradiated at a time. Thus, at large scale synthesis, exactly the same heat profile can be maintained. The major drawback with some reactions is that, not all substances are in solution prior to, or after, microwave irradiation and this can cause the flow to stop, due to blockage in pipes[17].

5 Application of Microwave Energy to Combinatorial Chemistry

Microwave-assisted solid-phase organic reactions have been the subject of several investigations during recent years[18]. Much of early work in this area was performed in domestic microwave ovens, which normally do not allow temperature measurements during the irradiation process and are not designed for scientific experiments, this causes the quality of the publications to greatly vary. Majority of publications have appeared as a communication or letter.

In order to achieve further development in this field, instead of domestic microwave oven, novel systems capable of proceeding reproducible results with minimal hazards should be used.

5.1 Solid Phase Synthesis

The ability to synthesize compounds on an inert polymeric resin bead, to force a reaction to completion by the addition of excess reagents and monomers, and to then remove all the unwanted material by a suitable filtration and wash, forms the core of most library synthesis[19-25]. The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research[26-28]. Combinatorial synthesis on solid support is usually carried out either by using parallel synthesis or the Furka split and mix procedures[29].

The combination of microwave power to solid phase synthesis is quite logical.[30] In several publications, significant rate accelerations and high loadings for several solid-phase protocols have been reported with reaction time being reduced in some cases from hours to a few minutes.

The combination of solid phase synthesis and microwave heating is receiving attention and this combination has enormous potential for better results.

Larhard *et al.*[30] have demonstrated that highly useful Suzuki and Stille reactions could be conducted under flash-heating conditions using a single mode cavity and would afford better yields. They reported microwave-assisted palladium-catalyzed coupling of aryl and heteroaryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored to Tenta Gels RAM, provided high isolated yields of coupled products after a reaction time of 3.8 min. Suzuki and Stille reactions worked readily on a polymeric support consisting of a benzoic acid linked to Rinkamide on polyethylene glycol (PEG) grafted polystyrene (Tenta Gel). The polymer was found to be stable under these harsh conditions[30] (Figure 3a and b).

Cotterill *et al.*[31] have successfully applied MICRO-COS technology (microwave-assisted combinatorial synthesis) to high throughput, automated, one step,

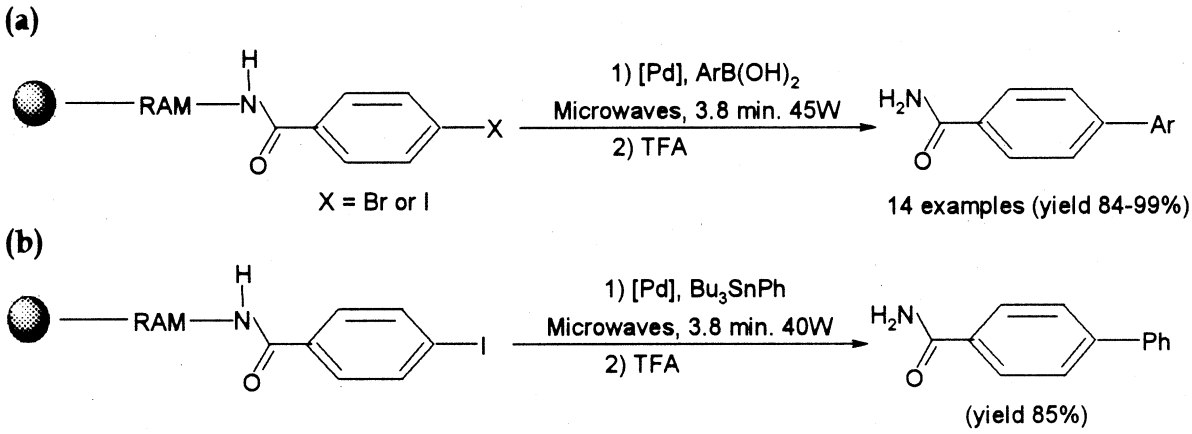


Fig. 3 — (a) Suzuki coupling on Solid-Phase Assisted by Microwave Irradiation. (b) Microwave assisted stille reaction on polymer tethered 4-iodobenzoic acid

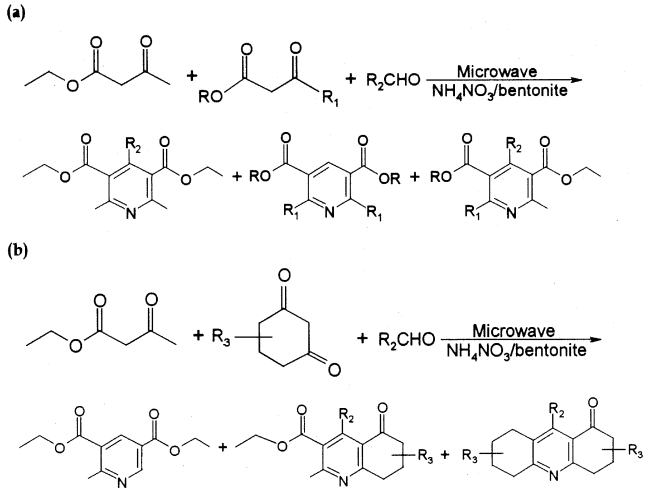


Fig. 4 — Microwave heating technique applied to high throughput, automated, one step, parallel synthesis of diverse substituted pyridines using Hantzsch protocol

parallel synthesis of diverse substituted pyridines, using Hantzsch synthesis the pyridine-scaffold is an essential structural element of many drugs. A solvent-free synthesis was performed in a 96-well format for the high-throughput automated production of diverse pyridines, which could be easily separated by HPLC. Each well of the glass, filled polypropylene 96-well filter plate reactors contained bentonite/ammonium nitrate as a support. Twelve aldehydes and eight 1, 3-dicarbonyl compounds were used as building blocks for library synthesis. The desired 1,3-dicarbonyl compounds and aldehydes distributed to each well of 96-well filter plate using robotic liquid handler. The 96-well reactor was then placed in a household microwave oven and irradiated for 5 min at 70 per cent power level. The plate was allowed to cool to room temperature and the wells were filled with 1mL ethyl acetate to extract the reaction products (Figure 4a and b).

Solid phase-solid state synthesis of *N*-alkyl imides from anhydride was first reported by Chandrasekhar *et al.*[32] γ-amino butyric acid was esterified with Merrifield resin, treated with phthalic anhydride and $TaCl_5$-SiO_2 and subjected to microwave irradiation after thorough mixing. After washing polymer bound imide was cleaved from resin by treatment with trifluoroacetic acid to furnish resultant product (Figure 5a).

Combs *et al.*[33] have reported the first examples of polymer supported aryl-hetero aryl C-N cross-coupling reactions and achieved dramatically reduced reaction times using microwave irradiation. *N*-arylated heterocycles comprise an important class of compounds often associated with biological activity. This reaction is α Cu (II)–mediated transformation and works well on polystyrene-PEG resin with a PAL-linker [an alternative to Rinkamide, based on 5-(4-aminomethyl-3, 5-dimethoxypheonoxy)-valeric acid]. The solid phase synthesis of *N*-arylated heterocycles has been demonstrated utilizing copper (II) mediated coupling of arylboronic acid to polymer bound benzimidazoles, imidazoles, triazoles and pyrazoles. During preparation of libraries of *N*-arylated heterocycles, 48 h cycle time was dramatically decreased using microwave irradiation. Irradiation of the polymer supported reaction in a domestic 1000 W microwave oven at full power for 3x10s, with manual agitation between each interval gave yields comparable to heating for 48 h at 80°C. The cycle time was effectively reduced from 48 h to less than 5 min (Figure 5b). Using 96-well micro-titer plates, an efficient method of library production was developed, although a considerable temperature gradient between

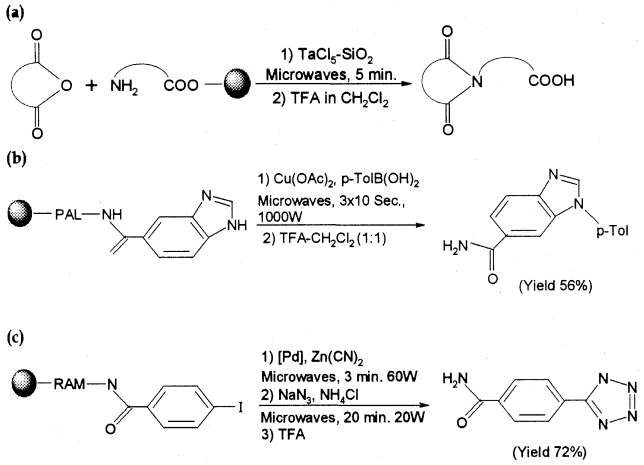


Fig. 5 — (a) Solid-phase solid state synthesis of N-alkyl imides from anhydrides, (b) Combs reported copper (II) mediated N-arylation of the benzimidazole with *p*-tolboronic acid, the first example of MICROCOS for N-arylated heterocycles, (c) Microwave-assisted heating technique is suitable for the conversion of iodides to nitriles and subsequently tetrazole

the inner and outer walls of the micro-titer plates was measured, using a thermocouple probe. Despite this non-uniform heating efficient library generation was obtained.

Alterman and Hallberg[34] have successfully reported fast microwave assisted preparation of aryl and vinyl nitriles and the corresponding tetrazoles from organo halides. Tetrazoles are of particular interest to the medicinal or combinatorial chemist because they constitute probably the most commonly used bio-isostere of the carboxyl group. Flash heating (20 W) in a single-mode cavity was successfully employed in the palladium-catalyzed conversion of various aryl and nitriles (Figure 5c). A low microwave power of 20 W was suitable for cycloaddition step of reaction.

In a recent study, Stadler and Kappe[35] have demonstrated that microwave irradiation can be effectively employed to attach aromatic carboxylic acids to chloromethylated PS resins via cesium carbonate method (Figure 6a). Using multimode microwave reactor, significant rate enhancement and higher loadings were observed when microwave – assisted protocol was compared with conventional thermal method. Reaction times were reduced from 12-48 h with conventional heating at 80°C to 5-15 min with microwave flash heating at 200°C in 1-methyl-2-pyrrolidone (NMP). No degradation of PS resin under prolonged exposure to microwave irradiation at 200°C was observed.

In a related study by same authors[36], they demonstrated that aromatic carboxylic acids could also be coupled effectively to PS Wang resin via the standard symmetrical anhydride protocol and microwave heating. Same loadings were observed in 1-methyl-2-pyrrolidone at 200°C within 10 min under atmospheric pressure, as opposed to 2-3 d using conventional coupling protocol at room temperature.

In an application of microwave assisted resin cleavage, reported by Glass and Combs[37], *N*-acylated amino acids attached to 4-sulphamyl butyryl resin were cleaved with different amines (Figure 6b). Cleavage rates in dimethylsulphoxide (DMSO) were investigated for di isopropylamine and aniline under different reaction conditions using both traditional oil bath heating and domestic microwave oven. Using the microwave approach, even cleavage with normally unreactive aniline could be accomplished within 15 min at 140°C. This principle was extended to the automated parallel synthesis of an 880-member library utilizing 96-well plates, employing 10 different amino acids (R_1) each bearing a different acyl group (R_2), and using 88 diverse amines (R_3R_4 NH) for cleavage.

A microwave–assisted parallel solid-phase synthesis of a collection of 21 polymer bound enones has been developed by Strohmeier and Kappe.[2] The two step protocol involves initial high-speed acetoacetylation of polystyrene wang resin with seven β-ketoesters (Figure 6c). When microwave flash heating at 170°C was employed, complete conversions were achieved within 1-10min., a significant improvement over the conventional thermal method, which takes several hours for completion. Significant rate enhancements were also observed for the subsequent microwave heated Knoevenagel condensations with a second set of 13 different aldehydes. Reaction times were reduced to 30-60 min at 125°C in the microwave protocol compared to 1-2 d, using conventional thermal conditions.

Scharn and coworkers[38] have prepared an 8000 member library of *tris*-amino and aminooxy-1,3, 5–triazines, using a highly effective microwave–assisted nucleophilic substitution procedure at cellulose-membrane-bound monochlorotriazines. Conventional heating protocol require harsh conditions such as a 80°C for 5 h or very long reaction times, i.e. about 4d, wheareas using microwave irradiation in a domestic oven under atmospheric reaction conditions, all substitution reactions were found to proceed within 6 min (Figure 6d). The reactions were carried out on 18

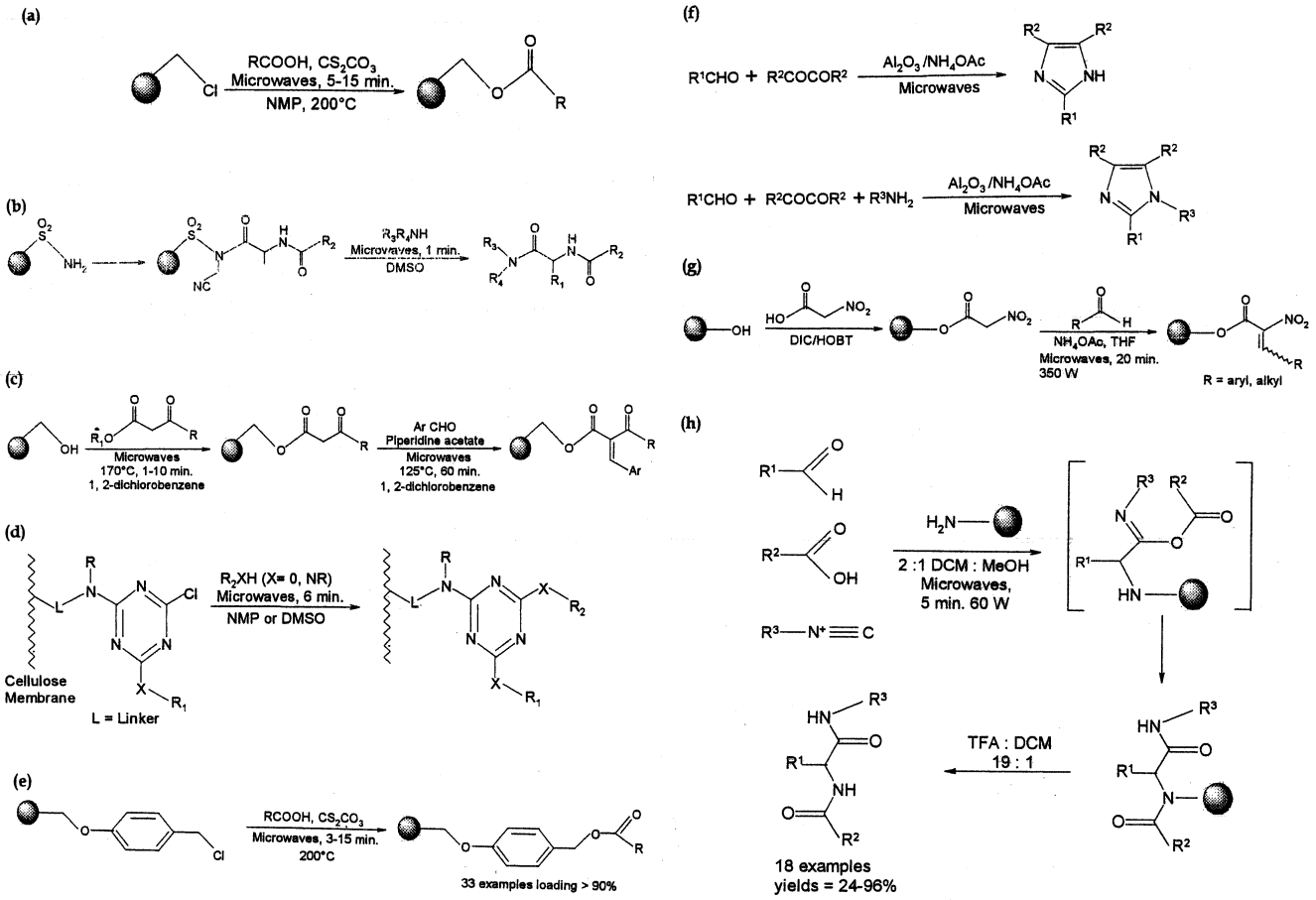


Fig. 6 — (a) Microwave-assisted solid-phase organic synthesis high speed coupling of aromatic carboxylic acids to chloromethylated PS resin at high temperatures, (b) Using microwave heating cleavage of N-acylated amino acids attached to 4-sulfamylbutyryl resin, with different amines, (c) Synthesis of polymer-bound inones utilizing microwave-assisted solid-phase chemistry, (d) The microwave-assisted substitution of the chlorine atom in mono-chlorotriazines, (e) More than 90% loadings achieved using microwaves in coupling of carboxylic acids to Merrifield resin. (f) Microwave-assisted synthesis of substituted imidazoles on a solid support under solvent-free conditions, (g) Preparation of resin bound nitroalkenes via microwave-assisted Knoevenagel reaction, (h) Microwave-assisted Ugi four component condensation (U-4CC), that can be used for preparation of known biologically active classes of compounds such as benzodiazepines, piperazines and lactams

X 26 cm cellulose membranes, leading to a spatially addressed parallel assembly of the desired triazines after cleavage with trifluroacetic acid vapour. This concept was extended to other halogenated heterocycles, such as 2, 4, 6 – trichloropyrimidine, 4, 6-dichloro-5-nitropyrimidine and 2, 6, 8-trichloro-7-methylpurine, and applied to the synthesis of macrocyclic peptidomimetics[39].

Use of microwaves in coupling of carboxylic acids to merrifield resin via their cesium salt significantly increase the extent of loadings as compared to conventional heating[37]. Loadings more than 20 per cent were achieved after only 3-15 min irradiation, time as compared with 12-48 h, when using conventional heating at 80°C (Figure 6e). No degradation of polymer resin during microwave irradiation was observed.

Usyatiasky *et al.*[40] have reported solvent-free microwave-assisted synthesis of 2, 4, 5 – substituted and 1, 2, 4, 5 – substituted imidazoles. Imidazoles were obtained as a result of the condensation of a 1, 2 – dicarbonyl compound with an aldehyde and an amine using acidic alumina impregnated with ammonium acetate as the solid support. They applied MICROCOS technology (Microwave–assisted combinatorial synthesis) to high throughput, automated, one-step parallel synthesis of diverse substituted pyridines using the Hantzsch synthesis (Figure 6f). The synthesis strategy was based on the condensation of 1, 2-diaryl-ethanedienones with aldehydes or aldehydes and amines resulting in 2, 4, 5 – substituted or 1, 2, 4, 5 – substituted imidazoles, respectively using

ammonium acetate as the ammonia source. HPLC purity of substituted imidazoles prepared by microwave–assisted method was between 75 to 85 per cent.

The preparation of resin–bound nitroalkenes via a microwave assisted Knoevenagel reaction of resin-bound nitroacetic acid with aryl and alkyl substituted aldehydes was described by Kuster and Scheeren[41] (Figure 6g). Nitroalkenes are versatile building blocks in the synthesis of many pharmaceutically interesting compounds. Several different resin bound nitroalkenes were prepared in one-step from resin bound nitroacetic acid with various aldehydes via a microwave assisted Knoevenagel reaction. In the first step, nitroacetic acid was attached to the polystyrene based Wang resin via a DIC/HOBT coupling reaction. Resin-bound nitroalkenes were formed in one step via a microwave assisted condensation (20 min, 350 W) of the aldehyde (10 equiv.) to the resin bound nitroacetic acid, followed by dehydration.

Hoel and Nielsen[42] have prepared an 18-member library from two isocyanides, three aldehydes and three carboxylic acids via microwave-assisted solid–phase Ugi reaction on Tenta Gel S RAM. Reactions where three or more reactants combine to give a single product, are known as multicomponent reaction (MCR). Among several useful reactions, Ugi four component condensation (U-4CC) in which an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide combine to yield an α-acylaminoamide, is particularly interesting due to the wide range of products obtainable through variation of the starting materials.[43] U-4CC can be used for preparation of known biologically active classes of compounds such as, 1,4-benzodiazepine-2,5-diones[44,45] diketopiperazines[46] and lactams[47]. Thus, U-4CC is ideal for use in the rapidly growing field of combinatorial chemistry. Products of high purity were obtained in moderate to excellent yields after reaction times of 5 min or less at 60 W (Figure 6 h).

5.2 Solution Phase Synthesis

Combinatorial compounds are created either in solution-phase or in solid phase. At its simplest level the solution-phase synthesis involves conducting solution-phase chemical reactions simultaneously preferably in well-ordered sets (arrays) of reaction vessel[48-52]. Combinatorial synthesis in solution can be used to produce libraries that consist of single compounds or mixtures using traditional organic chemistry[53]. Many researchers have successfully reported libraries of compounds prepared using solution-phase microwave – assisted synthesis.

Generally lead optimization is limited by speed of orthodox organic synthesis. Use of microwaves here accelerates the analogue synthesis and thus plays an important role in drug discovery. Selway and Terrett[54] have used microwave irradiation to achieve quick and convenient alkylation of 60 piperidines and piperazines to generate a library using parallel synthesis (Figure 7a). The library was screened in a herpes simplex virus (HSV-1) helicase ATPase assay and confirmed hits were identified.

In the search for new CNS-active drugs, Olsson *et al.*[55] have extended the procedure developed by Varma and Kumar[56] for thioamide synthesis that relies on Lawesson's reagent, and produced a library of 25 thioamides from the corresponding amides by a solvent-free parallel synthesis (Figure 7b). After extraction of solid-phase, products with adequate purity for use in HTS (High Throughput Screening) were obtained.

Habermann *et al.*[57] employed microwave irradiation in sealed vessel to epimerize the α-pyridyl proton of endo-epibatidine to the more thermodynamically stable exoisomer of epibatidine. (Figure 7c). Potassium *tert*-butoxide, in 30 h could not drive this process beyond 50 per cent completion, however, use of microwave irradiation enables conversion to 3 : 1 (exo:endo) ratio in favour of desired exo-isomer.

Kappe and Verma[58] have synthesized 4-aryl-3,4-dihydropyridinones using a Biginelli multi-component Biginelli condensation reaction. Mixture of aryl aldehydes, β-ketoesters and urea derivatives, in the presence of polyphosphate ester as the reaction mediator subjected to microwaves for 1.5 min, resulted in moderate to high yields (Figure 7d).

Varma[59] has employed solvent free conditions for multi-component reactions that leads to generation of imidazo-annulated pyridines, pyrazines and pyrimidines. These Ugi reactions, using clay as inorganic support are suitable for high speed parallel synthesis and library generation (Figure 7e).

A series of dihydropyrimidines utilizing the Biginelli multi-component reaction was reported by Stadler and Kappe[60]. A diverse set of 17 CH-acidic carbonyl compounds, twenty five aldehydes and eight urea/thioureas was used in the preparation of a dihydropyridine library. Out of full set of 3400 possible dihydropyrimidine derivatives, a representative subset of 48 analogs was prepared using automated addition

of building blocks and subsequent sequential microwave irradiation of each process vial (Figure 7f). Employing 10 min of microwave flash heating at 120°C leads to average yield of 52 per cent of dihydropyrimidines with more than 90 per cent purity.

A novel method for the synthesis of a library of substituted prolines utilizing microwave–assisted synthesis was described by Wilson *et al.*[61] The process involves rapid microwave irradiation of α-aminoesters and aldehydes to generate imines followed by the addition of a dipolarophile and subsequent irradiation to produce the [3+2] cycloadducts. The decrease in reaction time afforded by microwave irradiation allowed for the production of an 800-membered solution-phase library in two-fold less time than by traditional thermal methods (Figure 7g). These products were purified by solid-supported reagent scavenging to furnish the desired products in high yields and purity.

Wilson *et al.*[62] prepared a library of 2-aminoquinolines utilizing microwave–assisted synthesis. The heterocyclic quinoline scaffold and derivatives occur in many natural products and drug-like compounds. The process involves rapid microwave irradiation of secondary amines and aldehydes to form enamines followed by the addition of 2-azidobenzophenones with subsequent irradiation to produce the 2-aminoquinoline derivatives. In this method the initially formed triazoline intermediates undergo a thermal rearrangement and intermolecular base-catalyzed cyclocondensation to produce a quinoline based pharmacophore combinatorial library (Figure 7h). Conventional heating methods can be used to synthesize 2-aminoquinolines, but only low to moderate yields are obtained even after prolonged heating. Purification of the products is accomplished in a streamlined manner using solid-phase extraction techniques to produce the desired products in high yields and purity.

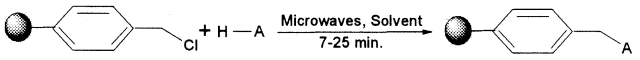
5.3 Preparation of Functionalized Resins

Functionalized resins have various applications in chemistry. They can be used as catalysts, polymer supported reagents, solid phase synthesis support and as scavengers in parallel solution-phase synthesis[63-67]. The wide acceptance of combinatorial technique for synthesis of molecular libraries and screening processes has stimulated the use of solid-phase organic synthesis (SPOS)[68].

First Publication about the use of microwave energy in preparation of functionalized resins for combinatorial synthesis was reported by Yang *et al.*[69] They synthesized a series of functionalized resins from merrifield resin by virtue of microwave irradiation.

Microwave irradiation dramatically enhance the reaction rates and achieve high conversions within 7-25 min (reaction 1). This method provides a convenient pathway for rapid preparation of solid-phase synthesis supports or scavengers.

5.4 Fluorous Chemistry

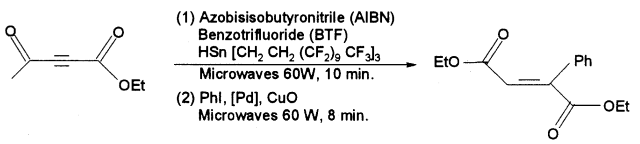


(1)

Fluorous synthesis the recently introduced technique capitalize on the immiscibility of highly fluorinated phases with organic solvents and water at room temperature[70]. Upon heating, molecules equipped with fluorous tags dissolve in organic solvents and combine with organic reactants, while upon cooling to room temperature, these fluorous molecules dissociate from organic phase and seek fluorous phase[71], thus facilitating purification. Fluorous techniques are able to speed the separation process to the point where the reaction time is the limiting factor in sample throughput in combinatorial or parallel synthesis. Focused flash-heating in monomode microwave oven is compatible with use of highly fluorous F-21 tags[72]. These reactions were sluggish under traditional thermal heating.

Reaction 2 comprises microwave promoted fluorous hydro-stannylation, followed by a Stille coupling of the resulting fluorous vinyl stannane with iodobenzene. The highly efficient purification procedures make the combination of fluorous chemistry and microwave flash heating attractive for combinatorial chemistry.

5.5 Polymer Supported Reagent



(2)

Apart from traditional solution-phase chemistry, application of polymer-supported reagents[73-75] (PSRs) are gaining considerable attention from combinatorial chemists.[76] The most important advantage of these

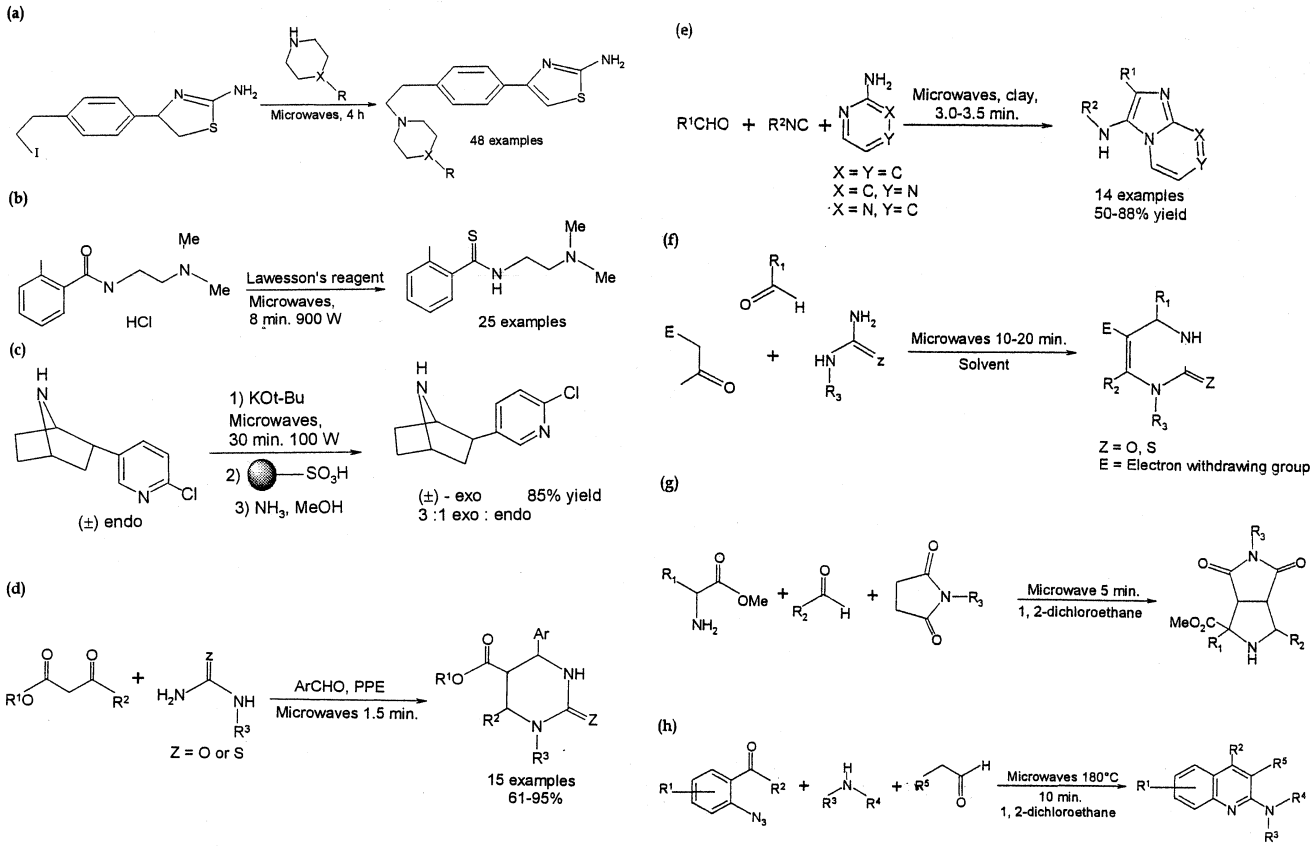


Fig. 7 — (a) Library of 48 antiherpes aminothiazoles prepared using microwave power, (b) Microwave accelerated solvent-free parallel synthesis of thioamides, (c) Synthesis of potent analgesic compound (+/-) epibatidine assisted by microwave energy, (d) Pharmacologically important dihydropyrimidinones synthesized by a microwave-promoted, solvent free modified Biginelli reaction, (e) Generation of imidazo-annulated pyridines, pyrazines and pyrimidines using microwave heating, (f) Using mono-mode microwave oven, the Biginelli multi component reaction leading to formation of multifunctionalized dihydro-pyrimidines, (g) Synthesis of substituted proline library using microwave irradiation, (h) Synthesis of 2-aminoquinolines library using microwave energy

reagent is the simplification of reaction work-up and product isolation, these processes being reduced to simple filtrations.

Brain *et al.*[77] have devised a rapid and efficient synthesis of 1, 3, 4 –oxadiazoles in high yields and purities by cyclodehydration of 1, 2-diacylhydrazines using polymer supported Burgess reagent under single-mode microwave conditions. Irradiation of various 1, 2-diacylhydrazines with a polyethylene glycol (PEG 750) supported Burgess reagent in tetrahydrofuran (THF) provided after only 2-8 min irradiation time the corresponding 1, 3, 4-oxadiazoles in 75-96 per cent yield and high purity Figure (8a) under conventional reflux conditions, a purification steps was only filtration through silica gel to remove soluble polymer-supported reagent, and evaporation of the solvent. In a variation of the above protocol, Brain *et al.*[78] has also reported the cyclodehydration of diacylhydrazines to oxadiazoles using the insoluble polystyrene (PS) – supported reagents B and C. Similar short reaction times (5-10 min) as with the soluble polymer support were achieved, using either of the two PS- supported reagents in THF with microwaves in sealed vessels.

Westman[79] has reported a novel one pot three-step Wittig reaction using polymer supported triphenyl phosphine under microwave irradiation (Figure 8b). Using single-mode microwave irradiation in closed vessel, desired olefins could be formed efficiently in just a few minutes employing a three component coupling process. The purity of so obtained olefins were excellent but yields were not always high (11-25 per cent).

Ley *et al.*[80] have reported the rapid conversion of amides to thioamides employing a PS-supported Lawesson-type thionating reagent. (Figure 8c). In

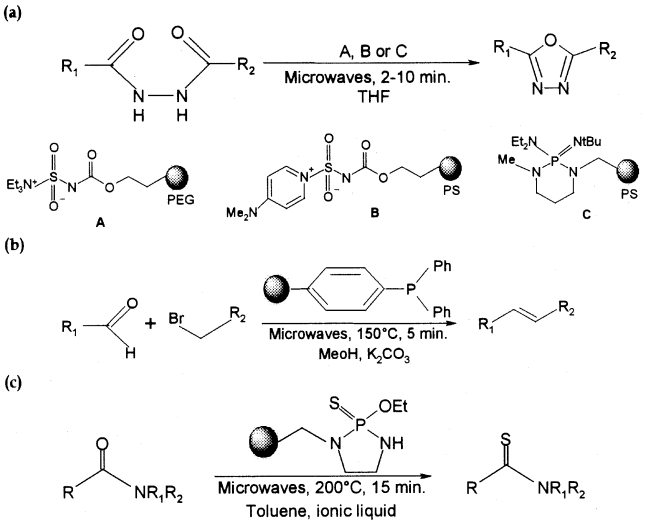


Fig. 8 — Polymer-supported reagents in microwave-assisted combinatorial synthesis, (a) Synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported burgess reagent under microwave condition, (b) Use of solid-supported triphenylphosphine for Wittig reactions under microwave irradiation. (c) Rapid conversion of amides to thioamides usingn PS-supported Lawesson-type thionating reagent

sealed vessels, employing mono-mode microwave oven (200°C), a range of secondary and tertiary amides was converted within 15 min to the corresponding thioamides in high yield and purity. Compared with classical reflux conditions, microwaves accelerated these thionation reaction the time being reduced from 30 h to 10-15 min. A small amount of ionic liquid (1-ethyl-3-methyl-1H-imidazolium hexafluorophosphate) was added to reaction mixture as toluene is not optimum solvent for absorption and dissipation of microwave energy, this ensures an even and efficient distribution of heat.

6 Conclusions

The use of microwave irradiation to provide activation energy leads to faster and cleaner reactions when compared to conventional heating. The impact of microwave technology to combinatorial synthesis includes increased diversity of libraries, simplified and efficient automation, dramatically increased synthetic throughput and simplified and efficient purification.

Reports on the successful use of domestic multimode ovens for library production are prevalent in literature but publications describing application of focused irradiation in single-mode cavities are steadily increasing because of efficient heat transfer and high reproducibility obtained.

Unfortunately, very few modern microwave reactors designed for safe automated synthesis, equipped with adequate and efficient temperature and temperature feedback control systems are currently available. New development in microwave reactors and vessel design are required with respect to scale up, higher-throughput in mono-mode cavities, more reliable parallel reactors with improved temperature control and specialized vessel design for solid-phase organic synthesis. Despite these limitations, use of microwave heating in combinatorial chemistry will continue to grow and is likely to become a standard procedure in coming years.

References

1 Kundu B, Khare S K & Rastogi S K, Combinatorial chemistry: polymer supported synthesis, *Prog Drug Res*, **53** (1999) 89.

2 Strohmeier G A & Kappe C O, Rapid parallel synthesis of polymer-bound enones utilizing microwave-assisted solid-phase chemistry , *J Comb Chem,* **4** (2002) 154-161.

3 Gedye R, Smith F, Kenneth W, Ali H, Boldisera L, Laberge L& Rousell J, The use of microwave ovens for rapid organic synthesis, *Tetrahedron Lett,* **27** (1986) 279-282.

4 Giguere R J, Bray T L & Duncan S M, Application of commercial microwave ovens to organic synthesis, *Tetrahedron Lett,* **27** (1986) 4945-4948.

5 Caddick S, Microwave assisted organic reactions, *Tetrahedron,* **51** (1995) 10403-10432.

6 Lidstrom P, Tierney J, Wathey B & Westman J, Microwave assisted organic synthesis- a review, *Tetrahedron,* **57** (2001) 9225-9283.

7 Wathey B, Tierney J, Lidstrom P & Westman J, The impact of microwave –assisted organic chemistry on drug discovery, *Drug Discovery Today*, **7** (2002) 373-380.

8 Galema S A, Microwave chemistry, *Chem Soc Rev*, **26** (1997) 233-238.

9 Baghurst D R & Mingos D M P, Superheating effects associated with microwave dielectric heating, *J Chem Soc Chem Commun,* (1992) 674-677.

10 Gabriel C, Gabriel S, Grant E H, Halstead B S J & Michael D, Dielectric parameters relevant to microwave dielectric heating, *Chem Soc Rev,* **27** (1998) 213-223.

11 Welton T, Room-temperature ionic liquid solvents for synthesis and catalysis, *Chem Rev,* **99** (1999) 2071-2083.

12 Mingos D M P & Baghurst D R, Application of microwave dielectric heating effects to synthetic problems in chemistry, *Chem Soc Rev*, **20** (1991) 1-47.

13 Strauss C R & Trainer R W, Developments in microwave-assisted solid phase chemistry, *Aust J Chem*, **48** (1995) 1665-1692.

14 Deshayes S, Liagre M, Loupy A, Luche J L & Petit A, Microwave activation in phase transfer catalysis, *Tetrahedron,* **55** (1999) 10851-10870.

15 Loupy A, Petit A, Hamelin J, Taxier B F, Jacquault P & Mathe D, New solvent-free organic synthesis using focussed microwaves, *Synthesis,* (1998) 1213-1234.

16 Kappe C O, High-speed combinatorial synthesis utilizing micro-wave irradiation, *Curr Opin Chem Biol,* **6** (2002) 314.

17 Cablewski T, Faux A & Stauss C R, Development and

application of a continuous microwave reactors for organic synthesis, *J Org Chem*, **59** (1994) 3408-3412.

18 Kappe C O, Speeding up solid-phase chemistry by microwave irradiation–A tool for high-throughput synthesis, *Am Lab,* **33** (2001) 13-19.

19 Lowe G, Combinatorial chemistry, *Chem Soc Rev,* **24** (1995) 309-382.

20 Terrett N K, Gardner M, Gordon D W, Kobylecki R J & Steele J Combinatorial synthesis-the design of compound libraries and their application to drug discovery, *Tetrahedron,* **51** (1995) 8135-8173.

21 Nefzi A, Ostresh J M & Houghten R A, The current status of heterocyclic combinatorial libraries, *Chem Rev,* **97** (1997) 449-472.

22 Dolle R E, Discovery of enzyme inhibitors through combinatorial chemistry, *Mol Diversity,* **2** (1997) 223-236.

23 Epton R, *Innovation and perspectives in solid phase synthesis and combinatorial libraries*, **1st ed** (Mayflower Scientific Limited, Birmingham) 1996, pp 5.

24 Szostak J W, Introduction: Combinatorial chemistry, *Chem Rev,* **97** (1997) 347-348.

25 Dorwald F Z, *Organic synthesis on solid-phase supports, linkers, reactions*, **1st ed** (Wiley-VCH, New York) 2001, pp 14.

26 Hermkens P H H, Ottenheijim H C J & Ress D, Solid phase organic reactions: a review of recent literature, *Tetrahedron,* **52** (1996) 4527.

27 Thomson L A & Ellman J A, Synthesis and application of small molecule libraries, *Chem Rev,* **96** (1996) 555.

28 Lam K S, Lebl M & Krchnak V, The one-bead-one-compound combinatorial library method, *Chem Rev*, **97** (1997) 411-448.

29 Edwards P, More microwave reactors required, *Drug Disc Today*, **6** (2001) 614.

30 Larhed M, Lindeberg G & Hallberg A, Rapid microwave-assisted suzuki coupling on solid-phase, *Tetrahedron Lett*, **37** (1996) 8219-8222.

31 Cotterill T C, Usyatinsky A Y, Arnold J M, Clark D S, Dordick J S, Michels P C & Khmelnitsky Y L, Microwave assisted combinatorial chemistry synthesis of substituted pyrimidines, *Tetrahedron Lett,* **39** (1998) 1117-1120.

32 Chandrasekhar S, Padmaja M B & Raza A, Solid phase-solid state synthesis of N-alkyl imides from anhydrides, *Synlett*, **10** (1999) 1597-1599.

33 Combs A P, Saubern S, Rafalski M & Lam P Y S, Solid supported aryl/heteroaryl C-N cross-coupling reactions, *Tetrahedron Lett*, **40** (1999) 1623-1626.

34 Alterman M & Hallberg A, Fast microwave assisted preparation of aryl and vinyl nitriles and the corresponding tetrazoles from organo halides, *J Org Chem*, **65** (2000) 7984-7989.

35 Stadler A & Kappe C O, High speed couplings and cleavages in microwave-heated, solid-phase reactions at high temperatures, *Eur J Org Chem*, (2001) 919-925.

36 Stadler A & Kappe C O, The effect of microwave irradiation on carbodiimide-mediated esterification on solid-support, *Tetrahedron*, **57** (2001) 3915-3920.

37 Glass B M & Combs A P, *Rapid parallel synthesis utilizing microwave irradiation in high-throughput synthesis principles and practices*, **1st ed** (Marcel Dekker New York) 2001, pp 123-128.

38 Scharn D, Wenschuh H, Reineke U, Schneider M J & Germeroth L, Spatially addressed synthesis of amino-and amino-oxy-substituted 1,3,5-triazine arrays on polymeric membranes, *J Comb Chem,* **2** (2000) 361-369.

39 Scharn D, Germeroth L, Schneider M J & Wenschuh H, Sequential nuceophilic substitution on halogenated triazines, pyrimidines and purines: a novel approach to cyclic peptidomimetics, *J Org Chem*, **66** (2001) 507-513.

40 Usyatinsky A Y & Khmelnitsky Y L, Microwave-assisted synthesis of substituted imidazoles on a solid support under solvent-free conditions, *Tetrahedron Lett*, **41** (2000) 5031-5034.

41 Kuster G J & Scheeren H W, The preparation of resin-bound nitroalkenes and some applications in high pressure promoted cycloadditions, *Tetrahedron Lett*, **41** (2000) 515-519.

42 Hoel A M L & Nielsen J, Microwave-assisted solid-phase ugi four-component condensations, *Tetrahedron Lett*, **40** (1999) 3941-3944.

43 Short K M, Ching B W & Mjali A M M, Exploitation of the ugi 4CC reactions: preparation of small molecule combinatorial libraries via solid phase, *Tetrahedron*, **53** (1997) 6653-6679.

44 Keating T A & Armstrong R W, A remarkable two step synthesis of diverse 1,4-benzodiazepines-2,5-diones using the ugi-four-component condensation, *J Org Chem*, **61** (1996) 8935-8939.

45 Hulme C, Peng J, Tang, S Y, Burns C J, Morize T & Labaudiniere R J, Improved procedure for the solution phase preparation of 1,4-benzodiazepine-2,5-dione libraries via armstrong's convertible isonitrile and the ugi reaction, *J Org Chem*, **63** (1998) 8021-8023.

46 Hulme C, Morrissette M M, Volz F A & Burns C J, The solution phase synthesis of diketopiperazine libraries via the ugi reaction; novel application of armstrong's convertible isonitrile, *Tetrahedron Lett*, **39** (1998) 1113-1116.

47 Harriman G C B, Synthesis of small and medium sized 2,2-disubstituted lactams via the intramolecular three component ugi reaction, *Tetrahedron Lett*, **38** (1997) 5591-5594.

48 Geysen H M, Armstrong R W & Kay B K, *Chemical diversity: the synthetic technique of combinatorial chemistry*, **1st ed** (American Chemical Society, Washington DC) 1995, pp 12.

49 Abelson J N, *Combinatorial chemistry*, **1st ed** (Academic Press, San Diego) 1996, pp 8.

50 Wilson S R & Czarnik A W, *Combinatorial chemistry synthesis and applications*, **1st ed** (John Wiley & Sons Inc, New York) 1997, pp 52.

51 Terrett N, *Combinatorial chemistry*, **1st ed** (Oxford University Press, New York) 1998, pp 25.

52 Czarnik A W & Dewitt S H, *A practical guide to combinatorial chemistry*, **1st ed** (American Chemical Society Washington, DC) 1997, pp 51.

53 Thomas G, *Medicinal chemistry an introduction*, **1st ed** (John Wiley & Sons Singapore) 1998, pp 86.

54 Selway C N & Terrett N K, Parallel compound synthesis: methodology for accelerating drug discovery, *Bioorg Med Chem Lett*, **4** (1996) 645-654.

55 Olsson R, Honsen H C & Anderson C M, Microwave-assisted solvent-free parallel synthesis of thioamides, *Tetrahedron Lett*, **41** (2000) 7947-7950.

56 Varma R S & Kumar D, Microwave-assisted solvent-free synthesis of thioketones, thiolactones, thioamides, thionoesters and thioflavanoids, *Org Lett*, **1** (1999) 697-700.
57 Habermann J, Ley S V & Scott J S, Synthesis of the potent analgesic compound (+/–) epibatidine using an orchestrated multi-step sequence of polymer supported reagents, *J Chem Soc Perkin Trans1*, (1999) 1253-1255.
58 Kappe C O & Varma R S, Microwave-assisted high-speed parallel synthesis of 4-aryl-3, 4-dihydropyrimidin-2-(1H)-ones using a solvent-less biginelli condensation protocol, *Synthesis,* (1999) 1799-1803.
59 Varma R S, Solvent-free synthesis of heterocyclic compounds using microwaves, *J Heterocycl Chem,* **36** (1999) 1565-1571.
60 Stadler A & Kappe C O, Automated library generation using sequential microwave-assisted chemistry application towards the biginelli multicomponent comdensation, *J Comb Chem*, **3** (2001) 624-630.
61 Wilson N S, Sarko C R & Roth G P, Microwave-assisted synthesis of a (3+2) cycloaddition library, *Tetrahedron Lett,* **42** (2001) 8939-8941.
62 Wilson N S, Sarko C R & Roth G P, Microwave-assisted synthesis of 2-aminoquinolines, *Tetrahedron Lett*, **43** (2002) 581-583.
63 Guillier F, Orain D & Bradley M, Linkers and cleavage strategies in solid-phase organic synthesis and combinatorial chemistry, *Chem Rev*, **100** (2000) 2091.
64 Simpson J, Rathborn D L & Billington D C, New solid phase knoevenagel catalyst, *Tetrahedron Lett*, **40** (1999) 7031-7033.
65 Sherrington D C, *Synthesis and separations using functional polymers,* **1st ed** (John Wiley & Sons, New York) 1988, pp 123.
66 Booth R J & Hodges J C, Polymer-supported quenching reagents for parallel purification, *J Am Chem Soc*, **119** (1997) 4882-4886.
67 Carpino L A, Mansour E M , Cheng C H , Williams J R, MacDonald R, Knapezyk J, Carman M & Lopusinski A, Polysyrene based deblocking-scavenging agents for the 9-fluorenylmethoxy-carbonyl-amino-protecting group, *J Org Chem,* **48** (1983) 661.
68 Dolle R E, Comprehensive survey of combinatorial library synthesis 2000, *J Comb Chem*, **3** (2001) 1.
69 Yang H, Peng Y, Song G & Qian X, Microwave-assisted preparation of functionalized resins for combinatorial synthesis, *Tetrahedron Lett*, **42** (2001) 9043-9046.
70 Curran D P, Strategy-level separations in organic synthesis: from planning to practice, *Angew Chem Int Ed Engl*, **37** (1998) 1175-1196.
71 Curran D P & Luo Z Y, Fluorous synthesis with fewer fluorines (light fluorous synthesis): separation of tagged from untagged products by solid-phase extraction with fluorous reverse-phase silica gel, *J Am Chem Soc,* **121** (1999) 9069-9072.
72 Olofsson K, Kim S Y, Larhed M, Curran D P & Hallberg A, High speed, highly fluorous organic reactions, *J Org Chem*, **64** (1999) 4539-4541.
73 Akelah A & Sherrington D C, Application of functionalized polymers in organic synthesis, *Chem Rev,* **81** (1981) 555-587.
74 Kaldor S W, Siegel M G, Fritz J E, Dressmann B A & Hahn P J, Use of solid supported nucleophiles and electrophiles for the purification of non-peptide small molecule libraries, *Tetrahedron Lett*, **37** (1996) 7193.
75 Parlow J J, Devraj R V & South M S, High-throughput purification of solution-phase periodinane mediated oxidation reactions utilizing a novel thiosulfate resin, *Tetrahedron*, **55** (1999) 6785.
76 Kirschning A, Monenschein H, & Wittenberg R, Functionalized polymers-emerging versaltile tools for solution-phase chemistry and automated parallel synthesis, *Angew Chem Int Ed Engl,* **40** (2001) 650.
77 Brain C T, Paul J M, Loong Y & Oakley P J, Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhyrazines using polymer-supported burgess reagent under microwave condition, *Tetrahedron Lett*, **40** (1999) 3275.
78 Brain C T & Bruton S A, Synthesis of 1,3,4-oxadiazoles using polymer-supported reagents, *Synlett,* (2001) 382.
79 Westman J, An efficient combination of microwave dielectric heating and the use of solid-supported triphenyl phosphine for witting reactions, *Org Lett*, **3** (2001) 3745.
80 Ley S V, Leach A G & Storer R I, A polymer supported thionating reagent, *J Chem Soc Perkin Trans, 1* (2001) 358.

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