The impact of microwave-assisted organic chemistry on drug discovery

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Microwave-assisted organic synthesis (MAOS) is rapidly becoming recognized as a valuable tool for easing some of the bottlenecks in the drug discovery process. This article outlines the basic principles behind the technology and summarizes the areas in which microwave technology has made an impact, to date.

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The first chemists, or alchemists as they were called, transformed one body into another by means of the elements, principally fire. Fortunately, fire is now rarely used but it was not until Bunsen invented the burner that the energy from this heat source could be applied to the reaction vessel in a focussed manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as sources of applying heat to a chemical reaction. The introduction of the isomantle required a fundamental change in the mind of the chemist, who now had to discard their favourite tool and turn to a safer more focussed alternative.

Recently, a new technique has come to the forefront of chemical research, microwave dielectric heating. In a similar way to the introduction of the isomantle, this technology will no doubt require a change in the chemist's mindset. In the future, the chemist will use quick bursts of microwave energy to heat and accelerate chemical reactions, instead of reaching in the first instance for the mantle or hot plate. In parallel with the use of solid-phase organic chemistry, microwave-assisted organic synthesis (MAOS) is now entering the new technologies arena as a *tour de force* in process, medicinal and combinatorial chemistry. We hope to demonstrate in this review the utility of this technique, and the potential that this methodology can give to the bench chemist.

Microwave heating

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

Developments in this field have suggested that microwave-assisted chemistry could be used in most reactions that require heating [1]. Microwave technology has been used in chemistry since the late-1970s, but it has only been implemented in organic synthesis since the mid-1980s. This slow uptake of the technology, when compared with computational or combinatorial chemistry, has been attributed principally to its lack of controllability and reproducibility, coupled to a general lack of understanding of the basics of microwave dielectric heating. However, since the mid-1990s the number of publications related to MAOS has increased significantly (Fig. 1).

Microwave theory

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radiowave. Microwaves have frequencies between 0.3 GHz and 300 GHz, corresponding to wavelengths between 1 mm and 1 m, respectively. Virtually all domestic and commercial equipment today uses a frequency of 2.45 GHz (wavelength 12.2 cm) for operation [2].

For a matrix to interact with microwave irradiation and generate heat, there are certain requirements that need to be fulfilled.

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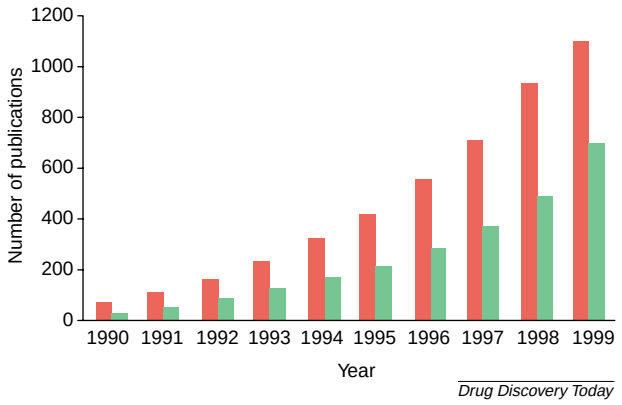

Figure 1. Growth in the number of published papers on microwave-assisted inorganic and organic chemistry. Accumulated number of papers (red) compared with the number of papers on organic synthesis (green).

First, the matrix must contain dipolar or ionic species to enable heating to occur. The heating occurs via two mechanisms – dipolar polarization and conduction. The dipoles or ions are induced to move in the matrix by interaction with the applied irradiation [3]. It is the electric field component of the microwave irradiation, rather than the 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. 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.

The movement of ions in the matrix by the interaction with microwave radiation is a much stronger heat generator than the corresponding motion of dipoles. Therefore, ionic species heat up extremely rapidly when exposed to microwave irradiation. This property of ionic species can be used to improve the heating ability of non-polar solvents upon exposure to microwave radiation.

When comparing the ability of different solvents to interact with microwave radiation, two important considerations are (1) the solvent's ability to absorb microwave energy and (2) its ability to convert the absorbed energy into heat. The interaction of a solvent with microwave irradiation is highly complex. As well as being dependent on the solvent's dielectric properties, which are in turn dependent on the temperature of the solvent and the frequency of the applied radiation, the interaction is also dependent upon the viscosity of the solvent (which is also temperature dependent). The best approximation for the comparison of different solvents is to compare their loss tangent values. The loss tangent (tanδ) is defined as the tangent of the loss angle (δ), which is the ratio between the dielectric constant, ε′ (which describes the solvent's ability to absorb microwave energy) and the loss factor, ε″ (which quantifies the efficiency with which the absorbed energy is converted to heat) (Eqn 1). Values of solvent loss tangents can be found in Table 1.

$$\tan\delta = \varepsilon''/\varepsilon' \qquad \text{[Eqn 1]}$$

The dielectric constants of acetone and ethanol, for example, are indeed in the

Table 1. Values of solvent loss tangents

Solvent	Dielectric constant (ε_s)[a]	Loss tangent (tanδ)[b]
Hexane	1.9	–
Benzene	2.3	–
Carbon tetrachloride	2.2	–
Chloroform	4.8	0.091
Acetic acid	6.1	0.174
Ethyl acetate	6.2	0.059
THF	7.6	0.047
Methylene chloride	9.1	0.042
Acetone	20.6	0.054
Ethanol	24.6	0.941
Methanol	32.7	0.659
Acetonitrile	36.0	0.062
Dimethyl formamide	36.7	0.161
Dimethyl sulfoxide	47.0	0.825
Formic acid	58.0	0.722
Water	80.4	0.123

[a]The dielectric constant, ε_s, equals the relative permittivity, ε′, at room temperature under the influence of a static electric field.
[b]Values determined at 2.45 GHz and room temperature.
Abbreviation: THF, tetrahydrofuran.

same range, but ethanol has a much higher loss tangent. For this reason, ethanol couples better with microwave radiation, resulting in a faster temperature increase.

Apart from the importance of the physical properties of the sample itself, the actual geometry and volume of the sample (load) are crucial to provide uniform and reproducible heating [4]. The volume of the load with respect to the oven cavity is referred to as the load volume and is more important than the geometry. Dramatic effects can occur when using load volumes greater or smaller than that specified by the manufacturer of the microwave apparatus. The heating of small samples can be especially troublesome, because they behave as if they are transparent to the microwave radiation. However, most of these problems can be overcome by the use of carefully designed cavities and vessels.

When the dielectric properties of the sample are too poor to allow efficient heating by microwave radiation, the addition of small amounts of additives (e.g. ionic salts) that have large loss tangent values can significantly overcome these problems and enable adequate heating of the whole mixture. This often provides an efficient way of using non-polar solvents for running syntheses using microwave radiation. However, solubility problems can result in heterogeneous mixtures that might cause problems in syntheses because of different degrees of heating. Furthermore, in some cases, an excessive amount of the additive that is large enough to alter the properties of the solvent has to be used. Therefore, a more efficient additive often needs to be used.

Fluid salts, or ionic liquids, consist entirely of ions and therefore absorb microwave radiation in a highly efficient manner. Many ionic liquids are particularly attractive additives because they are relatively inert, are stable at temperatures up to 200°C and have a negligible vapour pressure [5,6]. Moreover, ionic liquids dissolve to an appreciable extent in a wider range of organic solvents than water and alcohols. Because ionic species interact more efficiently with microwave radiation, ionic liquids that are soluble in non-polar organic solvents can be used as highly efficient additives to increase microwave absorption.

Since the early reports [7,8] of microwave organic synthesis, there have been many claims of a specific 'microwave effect' responsible for the observed rate accelerations [9,10]. In some circumstances, microwave heating can be rapid, producing heat profiles that are not easily accessible using other heating techniques. Therefore, experiments performed using MAOS might well result in a different outcome to conventionally heated reactions, even if the final temperature is the same.

One phenomenon encountered when performing microwave heating is that the boiling points of solvents can be raised up to 26°C above their conventional values; this is known as the superheating effect [3,11]. This higher boiling point can be maintained in pure solvents for as long as the microwave radiation is applied. However, substrates or ions that are present in the 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. It now appears to be accepted that the different temperature regime caused by microwave dielectric heating is the main contributing factor to any rate acceleration observed in MAOS [4,9,12].

The drug discovery process

MAOS can make an impact in several areas of drug discovery and is not only confined to areas related to organic synthesis. Microwave technology is also being used in target discovery, screening, pharmacokinetics and even in the clinic.

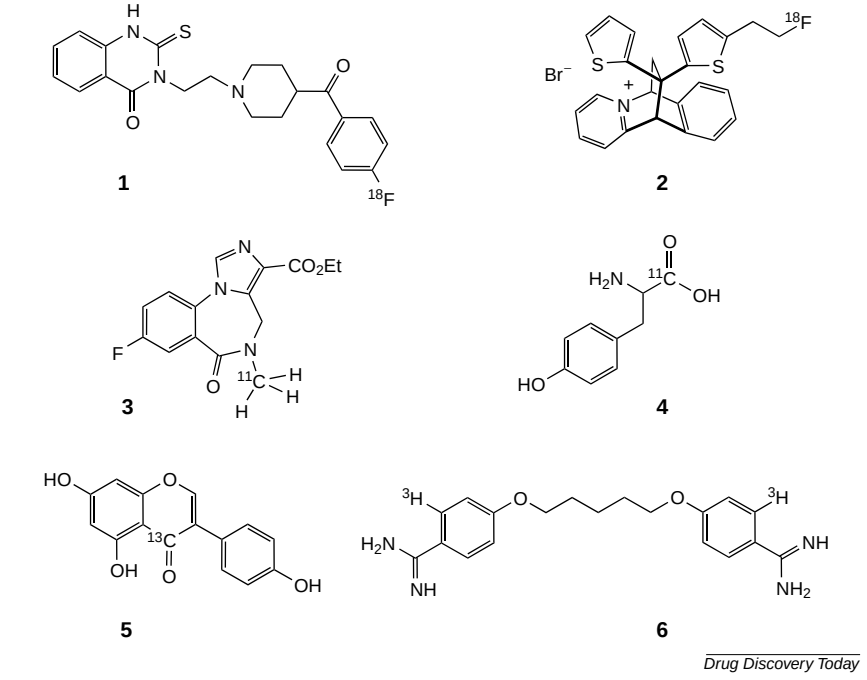

Figure 2. Isotopically labelled compounds prepared by microwave-assisted organic synthesis.

Screening and target discovery

The extremely short reaction times facilitated by MAOS enables short-lived compounds to be synthesized that could not otherwise be prepared using classical methods [18]. One interesting application of activation by MAOS is in the preparation of radiopharmaceuticals that contain isotopes with short half-lives (Fig. 2; e.g. ^{11}C,^{122}I and ^{18}F). In these examples, MAOS has been successful in reducing reaction times by up to 50% and has, in some cases, doubled the radiochemical yield of the final product.

Probably the earliest use of microwave-enhanced radiochemistry was in the synthesis of positron emission tomography (PET) pharmaceuticals for immediate use in human PET and *in vivo* rat imaging studies. The first use of microwaves in PET was reported in 1987 [13]. Since then, several microwave-assisted radiolabelling procedures have been reported [14]. The synthesis of PET radiopharmaceuticals has been achieved using monomodal instruments, which are optimized to heat small volumes efficiently. With these systems, not only are reduced reaction times and increased yields obtainable, but, most importantly, a high level of reproducibility is achievable. This reproducibility aspect is most important for PET radiopharmaceuticals that are required for human studies, for which the use of validated reproducible procedures is a requirement for compliance with good manufacturing practice regulations.

MAOS has found use in the preparation of ^{18}F-labelled radiopharmaceuticals [14], for example, the synthesis of [^{18}F]altanserin (Fig. 2; **1**) [15] and a new fluorine-substituted ligand (Fig. 2; **2**) of NMDA receptors [16]. Using microwaves, the time taken to produce and isolate the fluorinated tracers is reduced by 25–50%. This time-saving is highly beneficial to the radiochemical yield, because much less of the radioactivity has decayed during the preparation of the tracer, thus facilitating the synthesis of molecules that would otherwise require lengthy preparation times.

The microwave-assisted introduction of ^{11}C is now commonplace and *O*-, *N*- and *S*-alkylation with either an alkyl halide or triflate are the most common methods used. This approach has been used to prepare ^{11}C-labelled molecules, such as the benzodiazepine-receptor antagonist *N*-methylflumazenil, (Fig. 2; **3**) [17] and tyrosine (Fig. 2; **4**) [18]. Syntheses of compounds labelled with the stable isotope ^{13}C, have been performed using cyanide-based chemistry to introduce the labelled carbon. This methodology is illustrated by the synthesis of the labelled isoflavinoid phytoestrogens (Fig. 2; **5**) [19]. There is a wide variety of methods for the tritiation and deuteration of organic molecules, although each methodology has its limitations [14]. The advent of ^{3}H-NMR spectroscopy, new transition metal catalysts and the use of microwave irradiation has resulted in most of these problems being overcome. This has been elegantly illustrated in the synthesis of the antimalarial drug, pentamidine (Fig. 2; **6**). In contrast to the lengthy six-step ^{14}C synthesis, a one-pot reaction using an encapsulated catalyst and microwave irradiation produced a metabolically stable tritium-labelled product with higher specific radioactivity [20].

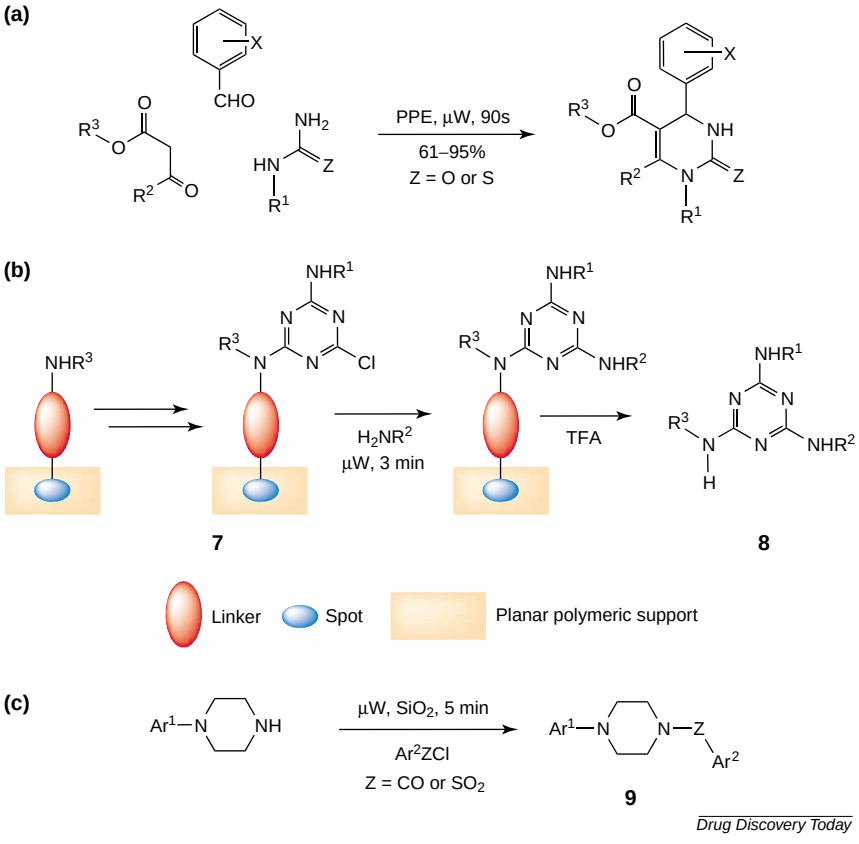

Figure 3. Examples of microwave-assisted parallel synthesis. **(a)** Biginelli reaction; **(b)** cellulose and polypropylene spot synthesis; **(c)** silica spot synthesis. Ar^1 and Ar^2 are various substituted aromatics. Abbreviations: PPE, polyphosphoric acid; TFA, trifluoroacetic acid.

Lead discovery

Microwave-assisted parallel synthesis

MAOS is a tool that is ideally suited to combinatorial chemistry. The first practical application of MAOS in

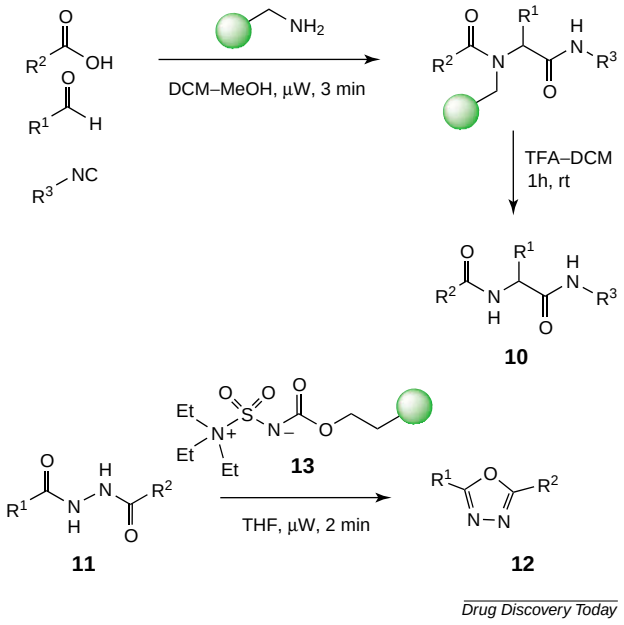

Figure 4. Examples of microwave-assisted solid-phase synthesis. Abbreviations: DCM, dichloromethane; TFA, trifluoroacetic acid THF, tetyrahydrofuran.

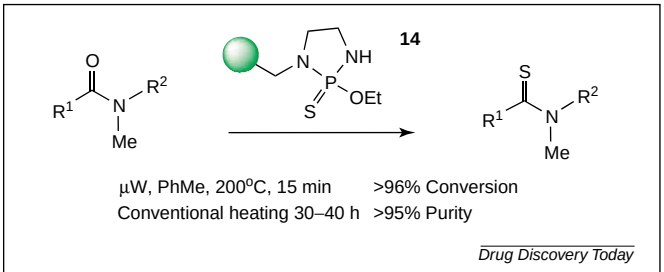

Figure 5. Solid-supported Lawesson's reagent equivalent.

microwave-assisted combinatorial synthesis (MICROCOS) is that described by Khmelnitsky *et al.* in which reactions were performed in a 96-well microtitre plate. They were able to produce libraries of diverse pyridines by high-throughput, automated, single step, parallel synthesis [21]. At present, the main use of MAOS for combinatorial chemistry and high-speed parallel synthesis is in the area of multi-component reactions, such as the Biginelli or the Ugi reactions. Kappe has published a pragmatic and effective Biginelli synthesis assisted by microwaves (Fig. 3a) [22]. The reactions were performed in open beakers placed in a domestic microwave oven; up to ten reactions could be performed in parallel in this manner.

In its most productive form, MICROCOS uses multi-component reactions for the synthesis of large and diverse libraries. A library of 8000 cellulose-bound triazines (Fig. 3; **8**) has been produced by applying the spot-synthesis technique to a cellulose or polypropylene membrane [23]. The key step in the production of this library was the microwave-assisted nucleophilic substitution of a membrane-bound monochlorotriazine (Fig. 3; **7**). A variation and extension to the spot-synthesis technique has been reported by Williams [24] (Fig. 3). This new procedure combines synthesis, purification, analysis and screening of combinatorial libraries, all on a single thin-layer chromatography (TLC) plate. After spotting the reagents on the baseline, the plate was irradiated with microwaves for five minutes (585 W) and cooled. The products were then eluted and isolated from the silica. A library of 40 *N*-substituted arylpiperazines (Fig. 3; **9**) was synthesized and purified for biological screening in 30 minutes. This methodology has been extended to incorporate screening by bio-autographical agar overlay [24].

Microwave-assisted solid-phase synthesis There are no reported examples of using microwaves to assist multi-step solid-phase or solution-phase library production, but microwave chemistry is undoubtedly being used by pharmaceutical companies to produce compound libraries. However, there are many examples in the literature where MAOS has been used to effect single transformations, using either solid-supported reagents or solid-supported substrates [1].

Microwave-assisted solid-phase synthesis (MASS) has been used to prepare an 18-member array of α-acylamino amides (Fig. 4; **10**) via a resin-bound Ugi reaction [25]. The products were obtained in moderate to excellent yield and in high purity, after a reaction time of less than five minutes with irradiation at 60 W.

Brain *et al.* have devised a rapid and efficient synthesis of 1,3,4-oxadiazoles in high yield and purity (Fig. 4; **12**). This reaction involves rapid cyclodehydration of 1,2-diacylhydrazines (Fig. 4; **11**) using polymer-supported Burgess reagent (Fig. 4; **13**) under microwave conditions [26]. Recently, Ley *et al.* have unveiled a clean polymer-supported equivalent to Lawesson's reagent (Fig. 5; **14**). Using this reagent, they have demonstrated an efficient odourless thionylating procedure under microwave conditions [27].

Lead optimization

MAOS is also starting to make an impact on medicinal chemistry. Kappe *et al.* have prepared the kinesin Eg5 inhibitor, monastrol (Fig. 6; **15**), under microwave conditions. By using a microwave-assisted Biginelli reaction they achieved a higher yield of the inhibitor with an improved purity profile, compared with the conventional synthesis method [28]. Kidwai *et al.* have shown microwaves to be effective in the synthesis of the novel antibacterial

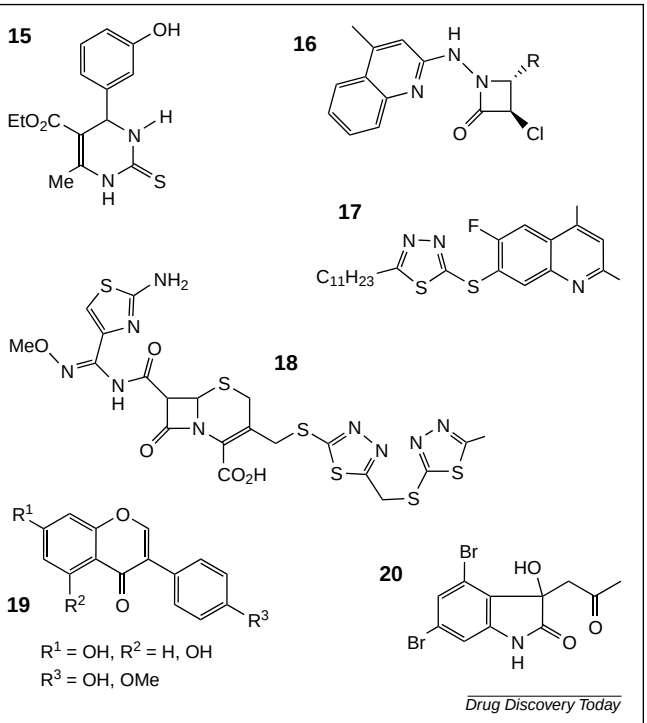

Figure 6. Examples of compounds synthesized with the use of microwave-assisted medicinal chemistry.

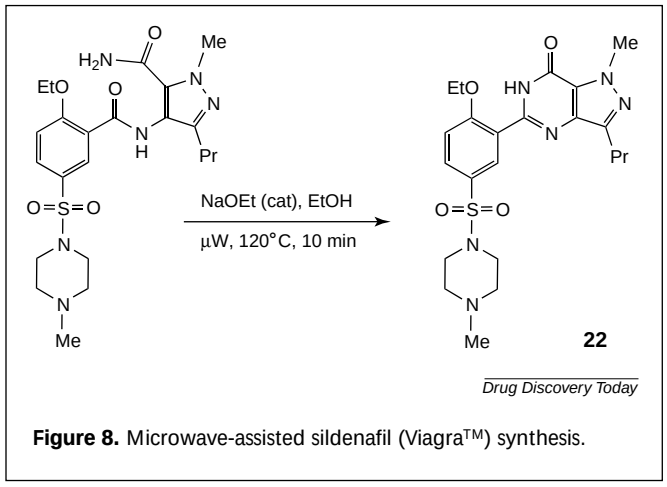

Figure 8. Microwave-assisted sildenafil (Viagra™) synthesis.

β-lactams (Fig. 6; **16**) [29], quinolines (Fig. 6; **17**) [30] and cephalosporins (Fig. 6; **18**) [31]. The synthesis of anti-carcinogenic soybean isoflavones (Fig. 6; **19**) [32], the anti-leukaemic alkaloid, convolutamydine-A (Fig. 6; **20**) [33] and the nitrogen mustard β-lactams and indoles [34] have also been reported to be enhanced by microwave irradiation (Fig. 6).

Hallberg *et al.* have described the use of microwave-promoted couplings in their 'fast synthesis' of modified HIV-1 protease inhibitors (Fig. 7; **21**). The palladium-catalyzed coupling of commercially available aryl and heteroarylboronic acids was effected by microwave irradiation (Fig. 7), enabling the synthesis and isolation of the desired compounds in high yields [35]. Ley and his group [36] have demonstrated the effectiveness of combining polymer-supported synthesis with microwave-assisted organic chemistry in the clean and efficient synthesis (Fig. 8) of the well-known commercially important pharmaceutical drug, sildenafil (Viagra™; Fig. 8; **22**).

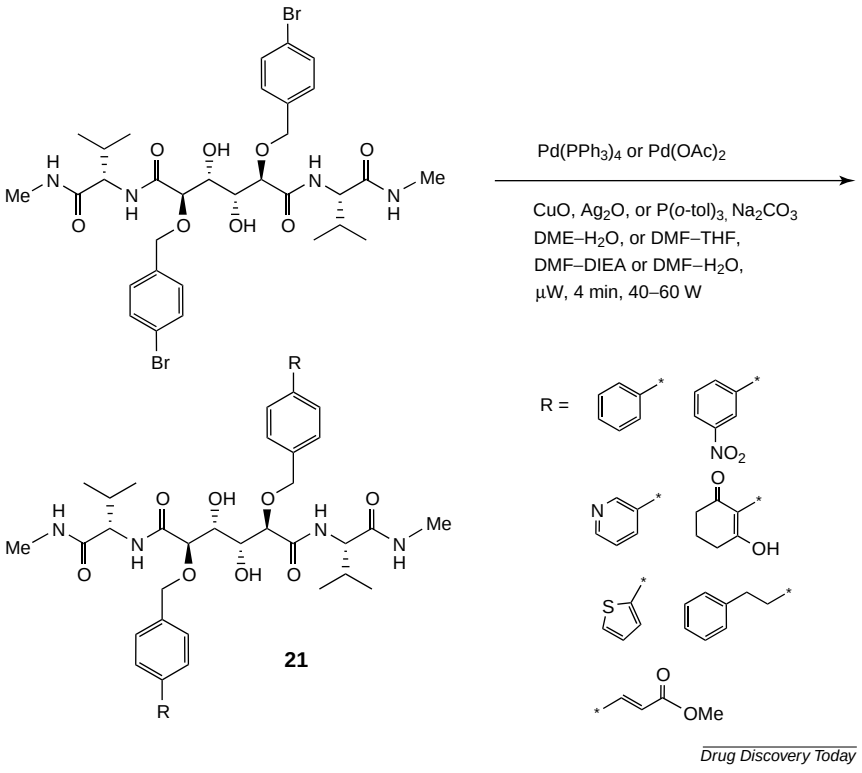

Figure 7. Hallberg's HIV-1 protease inhibitor synthesis. Abbreviations: DIEA, diisopropyl ethylamine; DME, dimethyl ether; DMF, dimethyl formamide; THF, tetrahydrofuran.

Drug development

The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when classical methods require forcing conditions or prolonged reaction times. Where processes involve sensitive reagents or there is a possibility of compound decomposition under prolonged reaction conditions, microwaves have also shown an advantage. The

use of focused microwave radiation to decrease reaction times and improve yields has recently been demonstrated (Fig. 9) in the multi-step synthesis of a thiazolo[5,4-*f*]quinazoline (Fig. 9; **23**) [37]. In contrast to conventional heating, using focused microwaves (irradiation in solution, 300 W) gave the desired compounds in higher overall yield with shorter reaction times and products that are more amenable to purification.

An interesting application of microwave activation is the epimerization of optically active compounds. A wide range of amino acids has been epimerized quantitatively within two minutes, thus avoiding the considerable decomposition that is associated with the use of classical heating [38]. Similarly, the complete epimerization of (–)-vincadifformine (Fig. 10; **24**) is achieved in <20 minutes to generate the (+) isomer (Fig. 10; **25**), which is subsequently used in the preparation of vincamine [39]. In contrast to MAOS, the classical conditions of prolonged heating for the epimerization, resulted in significant amounts of decomposition products.

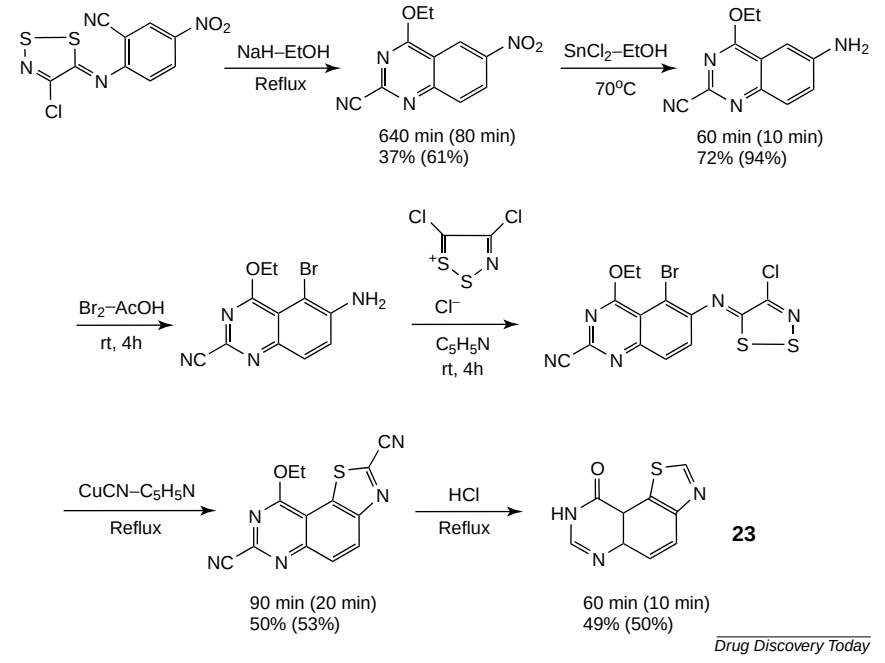

Figure 9. Microwave assisted synthesis of a thiazol[5,4-*f*]quinazoline. Numbers in brackets refer to the yields and reaction times obtained under microwave irradiation compared with conventional heating.

Other applications

Virus inactivation

Proteins derived from human plasma and proteins of pharmaceutical interest that are derived from mammalian cell culture can be contaminated with viruses. Heat inactivation of viruses is an attractive, non-invasive physical treatment of such proteins. Unfortunately, proteins are unstable at elevated temperatures for extended times and, therefore, during large-scale virus inactivation, temperature gradients in the vessel can present a problem for appropriate validation. It has been shown that microwave heating can be used to provide high-temperature, short-time heat treatment of streaming product fluids at flow rates of up to 8000 ml h^{-1} (J.K. Walter; unpublished data). The inactivation of various viruses that are typically used as model viruses in validation studies has been investigated and it was found that complete inactivation of enveloped and large non-enveloped viruses occurred at temperatures >75°C, whereas the non-enveloped virus (simian virus 40) was inactivated by >4.9 log at 86°C. The small, non-enveloped porcine parvovirus (PPV) was inactivated by 4.5 log at 97°C.

DNA preparation for the polymerase chain reaction (PCR)

Microwave irradiation has proved to be useful in DNA extraction protocols from different eukaryotes [40], and has also been demonstrated to be effective as a pre-treatment for the DNA extraction from plants and protists, before PCR amplification. It is assumed that microwave irradiation acts by exposing the DNA that is usually protected by cell structures.

Extraction

Solvent extraction of samples is often the first step in the analytical procedure following sampling. Common methods, such as Soxhlet extraction, are time consuming and use large amounts of solvents. Microwave-assisted extraction allows simple, rapid and low solvent-consuming extraction methods. This technology is particularly useful

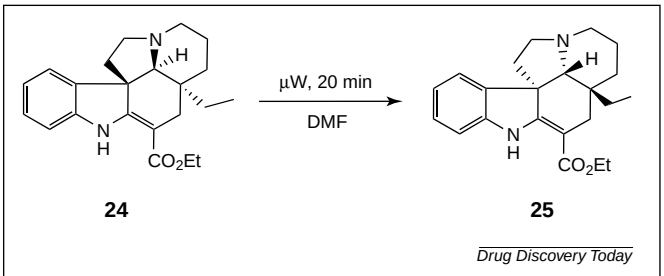

Figure 10. Epimerization of (–)-vincadifformine.

in the extraction of particulate-associated and semi-volatile compounds collected on filters and adsorbents such as polyurethane foam.

Microwave heating in immunohistochemistry

Temperature-controlled microwave technology has been used to accelerate immunohistochemistry [41]. Irradiation shortens the time needed for the immunostaining procedures by at least 20 times, while still retaining staining quality.

Conclusions

In this article we have tried to give a brief overview of where MAOS can ease the bottlenecks within the drug discovery process. Many of the early transformations were performed on simple or 'adapted' domestic instruments. The emergence of this technology over the past five years has seen several commercial instruments become available to the bench chemist. These instruments should provide solutions to the problems of reproducibility, controllability and safety experienced with the domestic microwaves. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Whether this potential is unleashed or not is dependent upon a change in the approach of the experimentalists.

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