Integrating Microwave-Assisted Synthesis and Solid-Supported Reagents

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6 Integrating microwave-assisted synthesis and solid-supported reagents

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6.1. Introduction

Microwave-assisted chemical processing has received a considerable amount of interest as a technology of the future since its instigation in the late 1980s[1,2] as an alternative heating method for organic reactions. Unfortunately, despite the potential revolutionising impact, microwave chemistry remained for many years more of an academic curiosity than a mainstream scientific tool. The historical reasons for this lack of acceptance are well known and have been extensively reviewed, and hence will not be covered here, except to state that they essentially revolved around the reproducibility of the experiments conducted. As a result, the area of microwave science as applied to organic synthesis remained rather dormant for over a decade. This period ended suddenly with the recent commercialisation of focused multi-mode applicator microwaves that are capable of operating at variable temperature and power settings. These machines have been specifically developed for the synthetic community so as to facilitate the rapid heating of organic reactions with the aim of enhancing productivity and shortening production times. Their introduction has significantly revitalised the general area and permitted microwave chemistry to become a mainstream tool of most bench chemists.

Despite the widespread adoption of this technology, we still do not possess a fully comprehensive knowledge of many of the fundamental aspects of microwave heating and its effects on the promoted chemistries. The area is still very much at an exploratory stage, where significant investigations have yet to be done to augment our understanding. For example, there remains a great deal of contention in the literature surrounding the possibility of rate enhancements due to athermal effects created by microwave irradiation[3–17]. The results and hypotheses from both sides of the discussion are very convincing, although with what amounts to a very small population of verified data it may be premature to draw absolute conclusions, as a number of authors seem apt to do. As with most emerging sciences, the reality will probably be more complex and less generic than the initial investigations seem to imply. This is certainly the case when considering the application of microwave heating to heterogeneous reactions in which significant differences are becoming apparent in the ways these systems can interact with microwave irradiation when compared to their more simplistic homogeneous counterparts. It is however evident, from nearly all the published work, that the application of microwave irradiation for heating chemical reactions is a useful approach for achieving higher reaction kinetics and the formation of cleaner products[18–24].

In addition to our interest in the use of microwaves for general synthetic chemistry[25–32], we have also been particularly intrigued with the potential benefits that could be realised by integrating them into our existing immobilised reagent methodologies and related synthesis platforms[24,33–36]. A significant problem encountered when using

supported reagents is the extended reaction times relative to their parent solution-phase equivalent. This reduced reactivity is unfortunately inherent with the immobilisation of the active species on a support material and its resulting heterogeneous nature. This effect therefore represents a significant technological challenge and a potential drawback to the continued development of the area.

In this chapter, we review and discuss some of the applications of microwave-related techniques to the area of accelerated synthesis using polymer-supported reagents. Besides a general description of working examples, we would also like to give a brief discourse on the current understanding and explanations for the reactivity observed. Not all the information contained within this chapter comes from referenced sources; there is an ever-increasing knowledge base of industrial expertise that we are fortunate to be aware of and would like to acknowledge Argonaut, AstraZeneca, GlaxoSmithKline, Millenium Pharamaceuticals, NovaBiochem, Novartis, Organon, Personal Chemistry and Pfizer. Although not peer reviewed by the wider scientific community, this information is still exceedingly valuable and is of a high standard given its economic importance.

6.2. Microwave heating of reactions

There are two distinct synthetic methods of applying microwave heating to reacting samples. The simplest is to conduct the reaction under normal atmospheric pressure in an open reaction vessel. This involves standard laboratory glassware fitted with a modified reflux condenser housed externally to the microwave cavity, using reaction temperatures at or just below the normal reflux point of the solvent. Although not strictly correct, this type of microwave reaction is becoming commonly known as MORE chemistry (microwave-induced organic-reaction enhancement)[37]; however, we feel these types of anagrams are not particularly helpful in defining the area[37–42] though these are frequently used. Even though this method is characteristically closer to standard synthetic methodology, it has been used significantly less than the alternative approach because of certain safety considerations. This alternative approach is microwave flash heating, a technique that utilises rapid heating and cooling of a sample contained in a sealed reaction vessel. In such processes, it is possible to generate high-internal pressures as a result of the elevated reaction temperatures employed, which are usually significantly higher than the standard boiling point of the solvent. This form of rapid thermal transition also seems to be beneficial with regard to the general integrity of the polymer matrix itself (including polymer-supported intermediates), which has increased stability under such short duration, high-pressure thermal exposure. This is certainly in contrast to many other reports that state that significant decomposition of immobilised starting materials and intermediates can occur with the action of prolonged conventional heating cycles at ambient pressure. For this reason, almost all the reactions involving polymer-supported reagents are now conducted using microwave flash heating.

6.2.1. *Heating a heterogeneous sample: polymer considerations*

When a sample containing a polymer-supported reagent is subjected to electromagnetic irradiation, it is possible for the energy to be directly coupled to polar functional groups. It then takes a defined period of time for the absorbed energy to dissipate

to the surrounding environment; this is especially pronounced if the majority of the polymer system has a low-thermal conductivity. Therefore, if the heat distribution time is greater than the time between heating pulses, thermal equilibrium is not reached and significant temperature variations can result. This gives rise to the phenomenon known as superheating[5,43,44]. This type of process has been proposed by Marand and co-workers[45,46] to explain the relative differences in microwave-dependent polymerisation experiments and later by Wei[47,48] to account for the relative rate enhancements in the thermal curing of epoxy resins. Indeed, extensive effort has been invested in the area of microwave curing applications, resulting in a number of interesting observations based on the increased reactivity of functionalised resins[45,46,49,50].

In general, when microwave heating leads to enhanced reaction rates, it is plausible to assume that the reactive sites on the surface of the polymer are subject to selective absorption, which could cause some pathways to predominate. This has certainly been seen in the case of many metal tethered or metal-impregnated catalysts. In these systems, the metal particles can be heated directly without notably heating the support because of their drastically different dielectric properties[51–54]. Roussy and co-workers have also described the effect of structural voids in materials, which can produce field non-uniformities in microwave heated samples resulting in temperature fluctuations[55]. Additional studies aimed at identifying and predicting the temperature variations in porous structures have concentrated on particulate metals immobilised within inorganic supports. These systems, usually comprising of small (1–5 mm) spherical pellets, have been used in continuous flow microwave reactors, and in general indicated only minimal microscopic temperature variations. There was, however, a strong dependence on the dielectric properties of the support material[56]. In cases where the inorganic matrix exhibited a high degree of 'lossy' character[57], only small temperature variations were noticed, but these became more pronounced as the absorption characteristics of the support became lower. This situation would be more representative of a functionalised polymeric resin, although the interaction and dissolution effects of any solvent present would significantly affect the microwave coupling ability. The speculation about the ability to selectively heat active sites to temperatures higher than the bulk surroundings is the subject of extensive research[58]. Such directed or localised superheating to create 'hot spots' by microwave irradiation is highly desirable as it represents a very simple and efficient method of supplying energy to the site of reaction, which otherwise cannot be achieved by conventional methods. Unfortunately, measuring the specific temperatures of individual active sites is beyond the current experimental capabilities and so is severely limiting the progress in this area. This area would offer enormous advantages for synthetic applications, especially for large-scale manufacture, if the required tuning and reproducibility can be obtained. In theory, only minor changes in local temperatures variations would need to be achieved to have quite drastic effects on overall chemical conversions, although these local heating effects can result in exponential reaction kinetics, raising some safety concerns.

6.2.2. *Heating a polymer-solvent: a binary phase system*

The interactive effect of the polymer and the solvent can be easily demonstrated in a very simple but crude microwave heating experiment, where no consideration is given

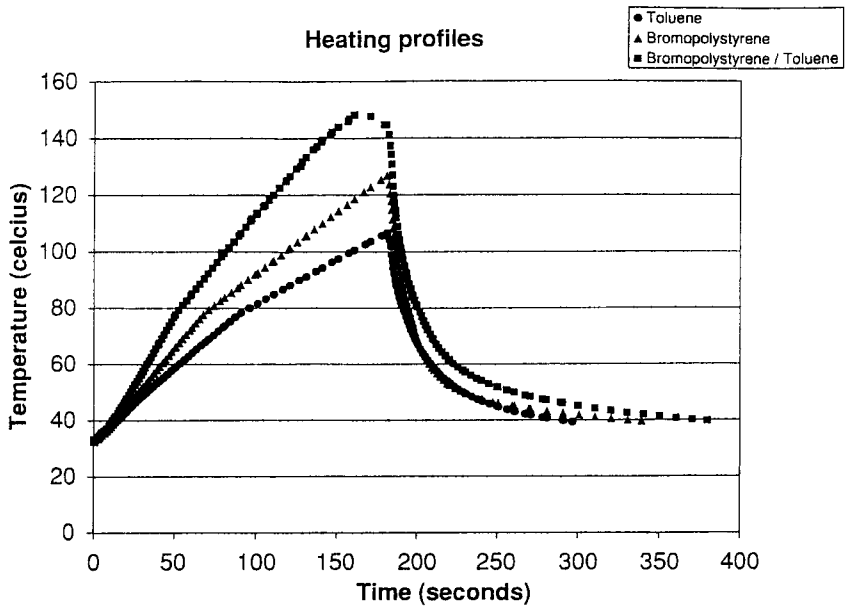


Figure 6.1 Heating profiles associated with the poorly absorbing solvent toluene and then the repeated heating showing the interaction of the solvent with a polymer resin.

to such factors as volume density, sample packing or irradiation penetrating differences. Presented in Fig. 6.1 are the heating profiles for three separate reactions involving the heating of (1) a sample containing neat toluene, (2) dry bromopolystyrene resin and (3) an equivalent weight of pre-swollen bromopolystyrene (toluene).

As can be seen from the data presented in Fig. 6.1, the heating profile of the pre-swollen resin is significantly enhanced in comparison to both the neat toluene and the dry resin samples. Of course, the swelling of the resin is a very important consideration, especially where a polar resin is being used because the charge distribution between the two phases will be enhanced (see later). This causes a difference in the sample's internal electric gradient that will affect the power absorption and ultimately the samples heating characteristics.

Many experimentalists are familiar with this principle of doping a sample with a species that couples better with the microwave irradiation and so can act as a thermal dissipater. What is often less appreciated is the general nature of this process, as not only solid/liquid interfaces but also liquid/liquid biphasic systems such as emulsions show the same effects[59–63]. Figure 6.2 represents the heating profiles of toluene and a perfluorinated solvent first independently and then as an emulsion. A similar trend can be seen in a hexane/acetonitrile mixture, although because of the superior heating capacity of acetonitrile the effect is less pronounced.

To place these results in context it should be reaffirmed that microwave heating is a completely distinct phenomenon operating in an entirely different way from microwave spectroscopy. This latter process involves the direct interaction of photons of a particular energy in order to excite the quantum rotational levels of gas-phase sample. Although in microwave heating, the absorption of microwave irradiation by a sample has been shown to be frequency dependent, it is not a requirement of the system for the energy to be quantised. As a result the heating process does not depend upon the direct absorption of microwave photons, instead the sample is heated via

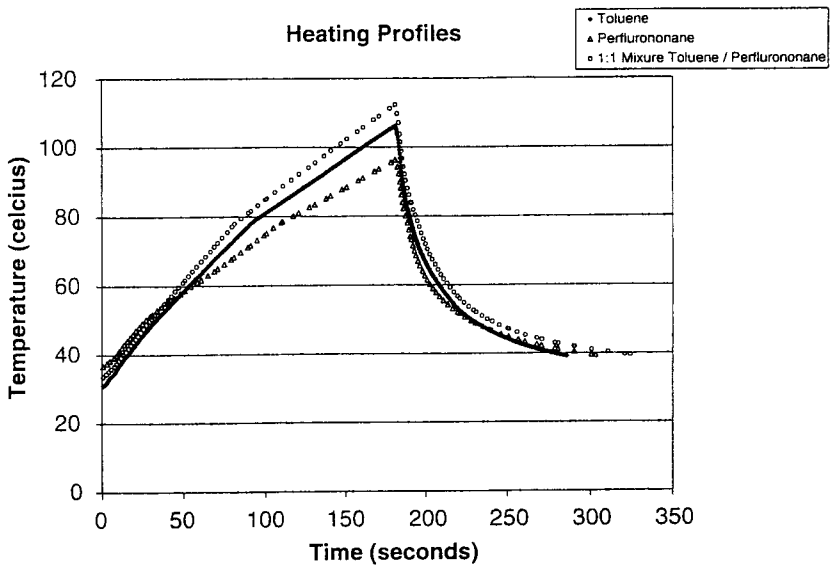


Figure 6.2 Doping effects of solvent combinations.

molecular interactions with the high-frequency electric and magnetic fields[64–67]. It is also understood that in biphasic systems the electrical properties of the two media (i.e., the electrical conductivity and dielectric constants) will differ and therefore the action of an applied electric field will be to induce electrical charges to appear at the boundary between the primary phase and the surrounding continuum. The distortion of the electrical double layer and the creation of Maxwell–Wagner interfacial polarisation will thus generate an electrical dipole moment[68–70]. Interestingly, the magnitudes of these induced dipoles are very large in comparison to those usually associated with molecular species because, although the magnitude of the charges involved may not themselves be large, the distance between their oppositely charged poles is by comparison a significant effect. As a consequence these induced dielectric properties cause enhanced and constructive wave interference within the sample leading to a more effective dielectric coupling and superior sample heating.

In addition the Maxwell–Wagner field theory also predicts that at the interface of two phases a proportion of the total microwave irradiation will be reflected. This can also be explained in terms of Snell's law of total internal reflection that describes the effect of altering the speed of photon movement between two media and is responsible for the bending (reflectance) of incident light. In this case although the emergent light's speed changes, as does the wavelength, the frequency remains constant ($\nu = f\,\lambda$). Considering the tremendous surface area and high-conformational diversity encountered throughout a polymer structure, we would expect a large number of interfacial combinations to be created in a system comprising of a polymer mixed with a solvent. Consequently, these phase boundaries would promote multiple internal reflections, thus increasing the available power absorbed before the radiation exits the sample. In effect this is equivalent to increasing the internal path length of the sample[59].

As these two aspects imply, the interaction of two phases can have a significant impact on the heating profile of a sample. It may also be of interest to consider the effect that the other reaction conditions, such as extremes of temperature and pressure, could have upon the development and continuation of such interfacial

effects (and the associated polarisation) during the reaction heating cycle. For example, as we will briefly consider later, the chemical nature and physical character of a solvent at non-ambient conditions can be substantially modified, therefore it is worth bearing in mind that as the reaction conditions change, so may the features of the solvent, which will alter the interaction with the secondary system.

6.2.3. *Migration of the reacting species*

The potential for reaction rate enhancement as a consequence of improved transport properties is an important consideration in any heterogeneous reaction. However, in the case of most supported reagent applications, an excess of the immobilised system is used (pseudo-first-order kinetics), making the requirements for diffusion less of a critical factor. Obviously, diffusion still remains a significant consideration for catalytic applications, as the rate of transportation of both reactants and products through the unreactive bulk remains an important issue. One area of interest is the altering of the diffusion dynamics that occur at the elevated operating temperatures and pressures encountered in many of the microwave-assisted reactions. A more intriguing question is: are there any additional advantages to be gained through the use of microwave irradiation? For example, can higher transport numbers be attained through enhanced organisation of the reactants or by selective activation of components within the mixture?

A number of authors have described noticeable improvements in the absorption/desorption and interaction of small organic molecules with polymeric systems under microwave heating conditions[71,72]. Many applications, including the industrial processing of textiles, where microwave irradiation has been shown to increase the fixing rate of dyes in polymeric fabrics[73,74] are encountered in the literature. However, the majority of the effects observed seem to be concerned with rapidly establishing equilibriums or the faster kinetics obtained at higher temperatures, rather than altering the mechanism of transport. This question has been examined in depth by Jeon and Kim[75], who determined that there was no discernible difference in the migration of simple organic solvents such as *n*-hexane, toluene, ethanol or carbon tetrachloride into polymer structures (polyethylene, PVC and silicone rubber), when compared to contemporary approaches based on classical thermal heating. The only differences they observed in absorption were related to the expected solvent swelling compatibility of the resins tested.

It is, however, worth noting that the gelling factors of many polymers are known to be affected under microwave irradiation, especially those systems comprising of very polar monomer units[76–79]. This can have a profound effect on the migration of reactants and products through the polymer structure and is especially associated with binary polymer systems, such as gel grafts, and other highly polar resins, such as polyacrylamide, where it can cause problems with reaction kinetics. In addition, dipole relaxation times can also become relatively large when a viscous or 'mobility'-restricting medium is involved. For example, if a polymer resin is introduced into a system, greater dielectric loss is observed. This has been extensively investigated only for systems containing soluble polymers[80–90], but the concept can be extrapolated to other resin environments as well. The origin of microwave heating lies with the ability of the electric field to induce a polarisation of charges within the heated sample. This induced polarisation due to the imposed restricted freedom of associated species

prevents it from following the rapid oscillations of the electromagnetic field, resulting in heating. Therefore, any change in the systems bonding from interactions with the polymeric support (more so in a polar medium) will significantly enhance dielectric loss and microwave coupling. This effect can also have important implications for the generation of hot spots and superheated areas, a concept we discuss later.

6.2.4. *Reaction heating: solvent considerations*

As previously stated, the selective heating of a single component can occur under microwave conditions; only components that couple with microwaves are directly heated. The non-absorbing components are thus heated indirectly by energy transfer from the other species. As is often the case in chemistry, the most suitable solvents for one aspect of a particular reaction are not usually the most effective for other reasons. Many of the typical solvents used in resin-based reactions are chosen for their effective resin swelling capabilities, but are often very poor microwave absorbers. (For reference there are three main microwave-related solvent characteristics: relative permittivity, dipole moment and the tangent delta—a term that defines the conversion of electromagnetic energy to thermal energy at a given frequency $\delta = \varepsilon''/\varepsilon'$, where ε'' is complex dielectric permittivity and ε' is dielectric loss. These components are related the absorbing ability of the solvent; see Chapter 1 for further details). There are a few exceptions to this statement such as *N*,*N*-dimethylformamide, 1,2-dichlorobenzene and acetonitrile, which can be successfully employed. But as already discussed, in a heterogeneous sample, such as a polymer suspension in a poorly absorbing solvent, heating is associated with the phase boundaries or specific interfacial topology. These regions, known as 'heating zones', are characterised by temperature gradients ranging in dimension from the macroscopic to the molecular scale. Furthermore, solvent pockets located deep within the confines of the resin can also experience the equivalent of a thermal squeeze, resulting from the difference in viscosity of the cooler external bulk solution and the expansion restricting nature of the resin channels. These small effects combined with restricted convection can produce temperature variations. This aspect of heating is of particular importance when products show thermal degradation, but require relatively high-activation energies for formation. Thus reaction in the superheated internal structure followed by migration of the product to the more temperate zones of the reaction media can enhance both the yields and the overall purity of the products.

The effect of solvent heating is obviously very important, because the temperature achieved is directly related to the speed of the reaction. It is therefore very significant that higher boiling points can be reached when solvents are subject to microwave irradiation in the absence of any mechanical stirring mechanism, even at atmospheric pressure. This effect, called superheating[5,43,44], is connected to both the chemical and physical properties of the solvent mixture and has been attributed to retardation of nucleation during microwave heating. Temperatures in excess of 20°C above the standard boiling points of certain solvents can be readily achieved (Table 6.1). These raised boiling profiles are created as a result of the propagation of microwave heating throughout the entire reaction volume and are related to microwave power levels[91–94]. As a consequence, a reverse heating gradient is produced in which lower temperatures are recorded at the periphery of the reaction vessel, due to energy dissipation to the surroundings, which is in

Table 6.1 Solvent boiling points (bp) at ambient temperature under normal thermal heating and under microwave conditions[43,91]

Solvent	bp (°C)	MW bp (°C)	Solvent	bp (°C)	MW bp (°C)
Water	100	104	Dichloromethane	40	55
Methanol	65	84	Chlorobenzene	132	150
Ethanol	79	103	1-Chlorobutane	78	100
Butan-1-ol	118	132	Trichloroethylene	87	108
Propan-2-ol	82	100	*N*,*N*-Dimethylformamide	153	170
Acetic anhydride	140	155	Acetone	56	81
Diglyme	162	175	Butan-2-one	80	97
Dimethoxyethane	85	106	Tetrahydrofuran	66	81
iso-Pentyl alcohol	130	149	Acetonitrile	81	107
iso-Propyl ether	69	85	Ethyl acetate	78	95

sharp contrast to classical heating procedures. The presence of materials that preferentially absorb microwave irradiation and exhibit 'lossy' character[56] can also lead to better conversions of the reactants and higher reaction rates. The application of highly absorbent materials such as graphite and amorphous carbon have also been used to create hot spot environments, which facilitate greater rates of reaction[95–104].

Under the appropriate conditions the support material can also act as the solvent. For example, a number of publications have described the use of soluble polymers, such as PEG, to serve as both phase-transfer reagents and the solvent for a reaction[105–115]. PEG systems of low-average-molecular weight offer a number of unique attractions because of their relatively low-melting points (MW 400–800) 45–47°C and facile separation from small organic compounds. Under the action of focused microwave irradiation, PEG can function as the solvent environment very effectively, absorbing microwave irradiation and diffusing the heat to the reactants. In addition, this solvent system can also effectively stabilise and support ionic species, especially cations, in a manner similar to more expensive crown ethers[116–118].

If such a chemical enhancement can be realised at ambient pressures, the significance is obviously going to be much greater when sealed reaction vessels at high temperatures are employed. In this case the dimensions of the reaction chamber, the volume of solvent and its specific boiling point and the final pressure reached will all affect the chemistry taking place. In fact, a direct relationship between the observed pressure and temperature and any rate enhancement can usually be made. An issue that needs additional consideration with regards to promoting homogeneous and heterogeneous reactions is the potential new properties of the solvent under these forcing conditions. The specific properties of a given solvent under standard conditions are well documented, but this is not as well defined when elevated temperatures and pressures are applied. Many of the microwave reactors are capable of running reactions at temperatures exceeding 250°C, with associated pressure containment to approximately 20 atm. Under such conditions, the behaviour and attributes of most solvent systems will be significantly different to their normal characteristics. This situation is well illustrated by methanol, which at high temperatures and pressures resembles a solvent more like hexane. For applications involving polymers, this can have a significant effect because of the difference in swelling ability and the solubility of the reactants and products. A

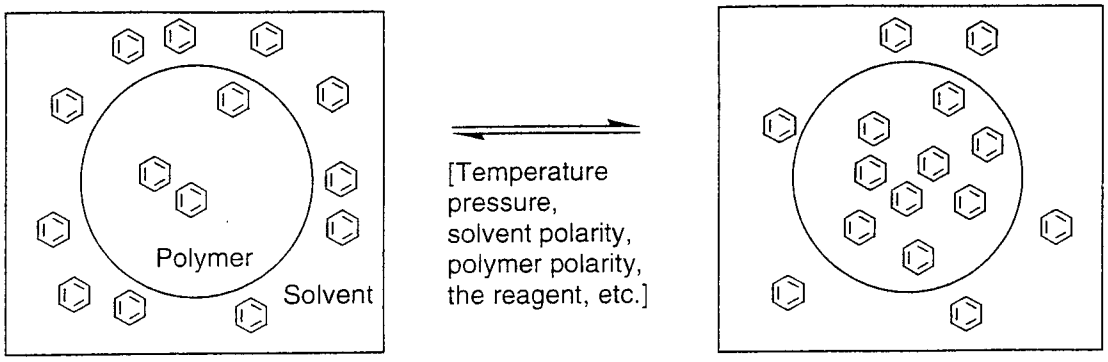


Figure 6.3 A cartoon representation depicting the equilibrium conditions of substrate or solvent molecule interacting with a polymer resin.

biphasic reaction containing a polymeric reagent as one component represents a series of dynamic equilibriums. In addition to any chemical equilibria established due to the interconversion of reactants and products, there are also a series of distribution equilibriums concerned with the varying solubilities and residence of the reacting components in the bulk solvent and the solvent-like polymer species (Fig. 6.3)[119]. Due to the phase boundary, these two environments are in direct competition for the smaller substrate molecules, which will affect both reactivity and product isolation. The solvent will be a critical factor that determines the levels of compartmentalisation. As with all equilibria, temperature and pressure can have a significant effect, but this will be multiplied if the properties of the solvent change (i.e., polarity and solubilising ability). In fact the retention of product within the resin is one of the most common reasons for the isolation of low yields from a resin-based reaction, even under ambient conditions. In addition, increased precipitation and crystallisation of materials involving polymer species is also quite common, because of the selective concentration of compounds into one phase. The situations in the pre-, post- and even during the microwave reaction will be radically different if flash heating techniques are applied. It will therefore often be essential to screen a range of solvents to identify the best combination for a specific reaction and resin type. Although this is a complication to the use of polymers with microwave heating, the possibility arises that these solubility differences and equilibriums can be harnessed to promote novel chemistry, which otherwise would not be possible.

6.3. Microwave reactions with polymer-supported reagents

There are only three partial reviews to date that mention the integrated approach of using polymer-supported reagents with microwave heating, which highlights the novelty and recent establishment of the field[120–122]. It is certainly evident from the growing interest in the two concepts that the complementary nature of their combined use will soon result in significantly more reports. In the following section, we review a number of the existing reactions and supplement them with a selection of related observations to provide a more comprehensive knowledge source for this exciting new field.

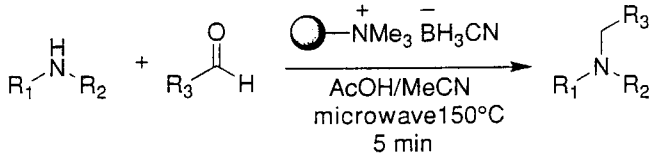
6.3.1. *Polymer drying*

The most basic application of microwave heating is in the rapid drying of resins prior to a given reaction. Many polymer reagents are exceedingly hydroscopic, and retained water can affect the properties of the reagent and its resulting reactivity. Extensive use has been made of domestic microwave units to dehydrate resins, especially polystyrene-based material, which are usually very poor microwave absorbers (although this is highly dependant on the loading and type of functionality). This poor absorbency in comparison to the residing water allows for selective heating of the matter resulting in rapid drying (this has also been conducted more effectively on a larger scale under reduced pressure). This approach has also been used for a number of inorganic supports and is a common practice for drying molecular sieves and silica samples.

6.3.2. *Reductive aminations*

It has long been known that imine formation can be rapidly achieved using microwave flash heating[123–125]. In many cases this process is facilitated by using suitable solvents like toluene, which allow the water to be driven from the reaction mixture by either azeotropic distillation or direct evaporation into the vapour phase as a result of selective heating. Chemists at GlaxoSmithKline have extended this coupling sequence to include a rapid reductive amination reaction, using an immobilised cyanoborohydride reagent[126]. In this way a small set of aldehydes and amines were successfully coupled and reduced using an automated microwave procedure (Scheme 6.1). It was noted that under the optimised conditions, a problematic side reaction occurred involving a competing acetylation of the secondary amine products by the acetic acid catalyst. This proved only a minor problem because purification could be easily achieved using an SCX scavenging protocol. This type of direct amide bond formation from an acid and amine has also been described in the literature and has proved to be very facile under microwave heating conditions[127]. One of the other competing reactions that has been identified using both the immobilised and solution-phase cyanoborohydride reagents under the high pressures and temperatures produced using microwave heating is the release of cyanide anion from the borohydride reagent. Although only a minor product, this still obviously indicates some potential health and safety considerations that need to be addressed before doing this transformation.

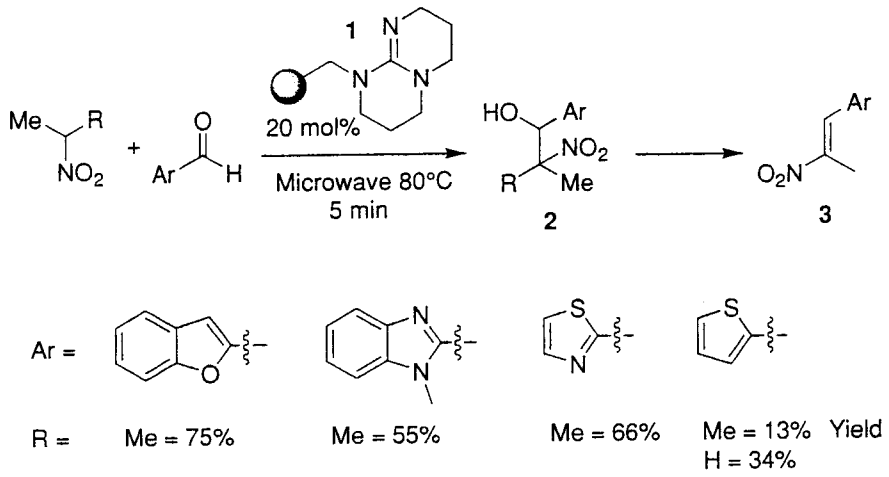
Many reductions have also been conducted under similar conditions using the simple immobilised borohydride resin. The majority of these reactions have been conducted because the corresponding room temperature reaction proved to be very slow. Again enhancements in rates and overall yields have been noticed.



Scheme 6.1

6.3.3. *The Henry reaction*

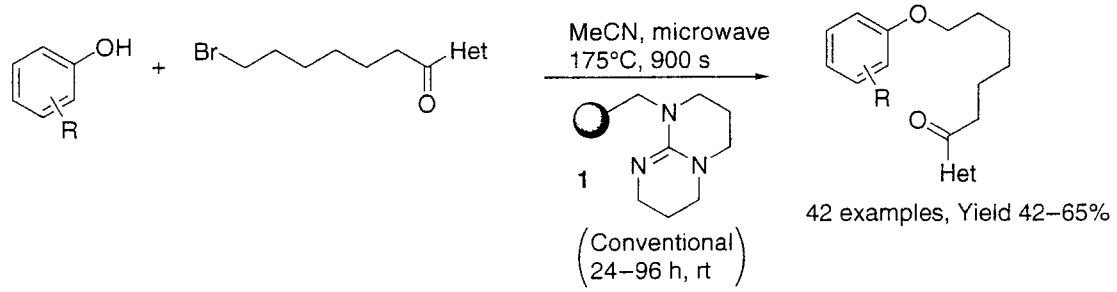
The nitro aldol (Henry) reaction is known to be successfully catalysed by many strongly basic ion exchange resins such as those functionalised with chloride or hydroxide ions[128]. More recently, the use of milder bicyclic guanidine bases including the supported TBD variant (1,5,7-triazabicyclo[4.4.0] dec-1-ene) **1** have been shown to be exceedingly effective for the same transformation[129]. In addition, these reactions tended to proceed with higher levels of chemical selectivity, favouring the nitro aldol adducts **2** over the further eliminated alkene by-products **3**. Using an immobilised guanidine reagent, therefore, combines the advantages of increased selectivity with the simplified purification protocols that are particularly important for parallel synthesis applications. Scientists from the pharmaceutical division of Aventis have taken this one step further and investigated this transformation under microwave heating conditions to expediate a more rapid generation of large libraries of intermediates for use as diverse starting materials in subsequent combinatorial programmes (Scheme 6.2)[130]. They reported that in a matter of a few hours, they were able to prepare a reasonably sized array of nitro-alcohols and the corresponding dehydrated β-nitro styrenes. Although no specific details were released regarding the exact distribution of the two possible products, the comment was made that the selectivity of the particular product isolated was very substrate dependent.



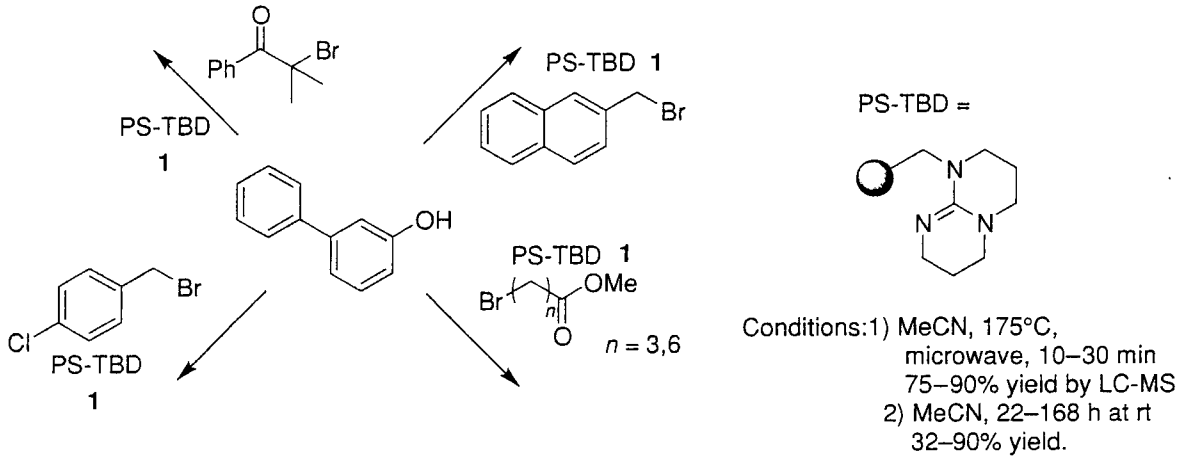
Scheme 6.2

6.3.4. *Alkylation reactions*

Researchers at Abbott Laboratories have also combined the use of the polymer-supported TBD base **1** and microwave irradiation for the alkylation of various phenolic components[131,132]. These reactions were conducted to evaluate the microwave procedure against the traditional literature conditions, which involved prolonged mixing at ambient temperatures (24–168 h). It was discovered that as expected, elevated temperatures significantly reduced the reaction times, but more significantly, the products in all but a couple of cases could be isolated in higher overall yields and significantly greater purity (Schemes 6.3 and 6.4).



Scheme 6.3



Scheme 6.4

This ability of microwave irradiation to facilitate higher and cleaner conversions seems to be a very common result. Many authors have reported similar improvements in isolated yields and purities in both their own work and in examples where microwave heating procedures have been applied to previous documented transformations. The majority of these improved experimental conditions usually involved microwave flash heating protocols. The principle rationalisation for the observed enhancement is the rapid and homogeneous heating of the sample to the desired reaction temperature, resulting in reduced time periods for alternative pathways to successfully compete. In other words, if one assumes that most purity-reducing reactions are as a result of the decomposition of the starting materials or product at less than optimal reaction temperatures then this would account for the improved product yield and composition. This type of near instantaneous heating and cooling as achieved through microwave heating of the sample is often referred to as the 'square' heating profile (Fig. 6.4). This partial explanation, although important, ignores many additional factors especially when heterogeneous systems are involved (see discussion in the previous sections).

6.3.5. *O-Alkylations of carboxylic acids*

Flash microwave heating of samples in sealed vessels has also been used by Linclau *et al.* to accelerate the rate of acid esterification reactions using an immobilised DCC derivative

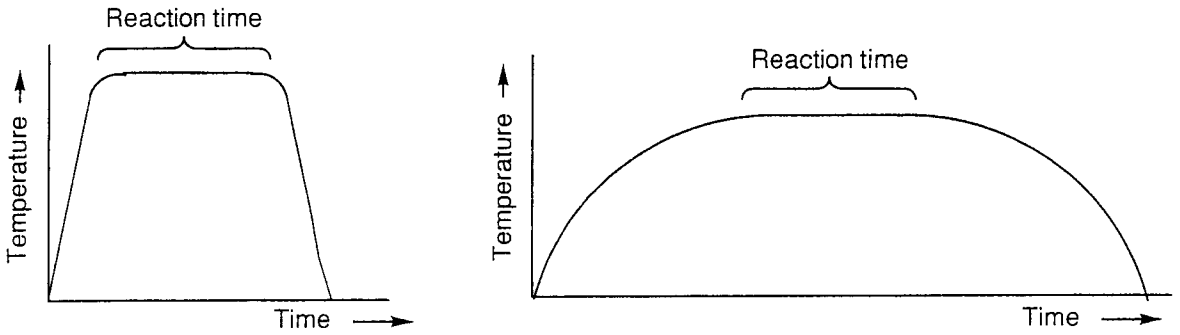
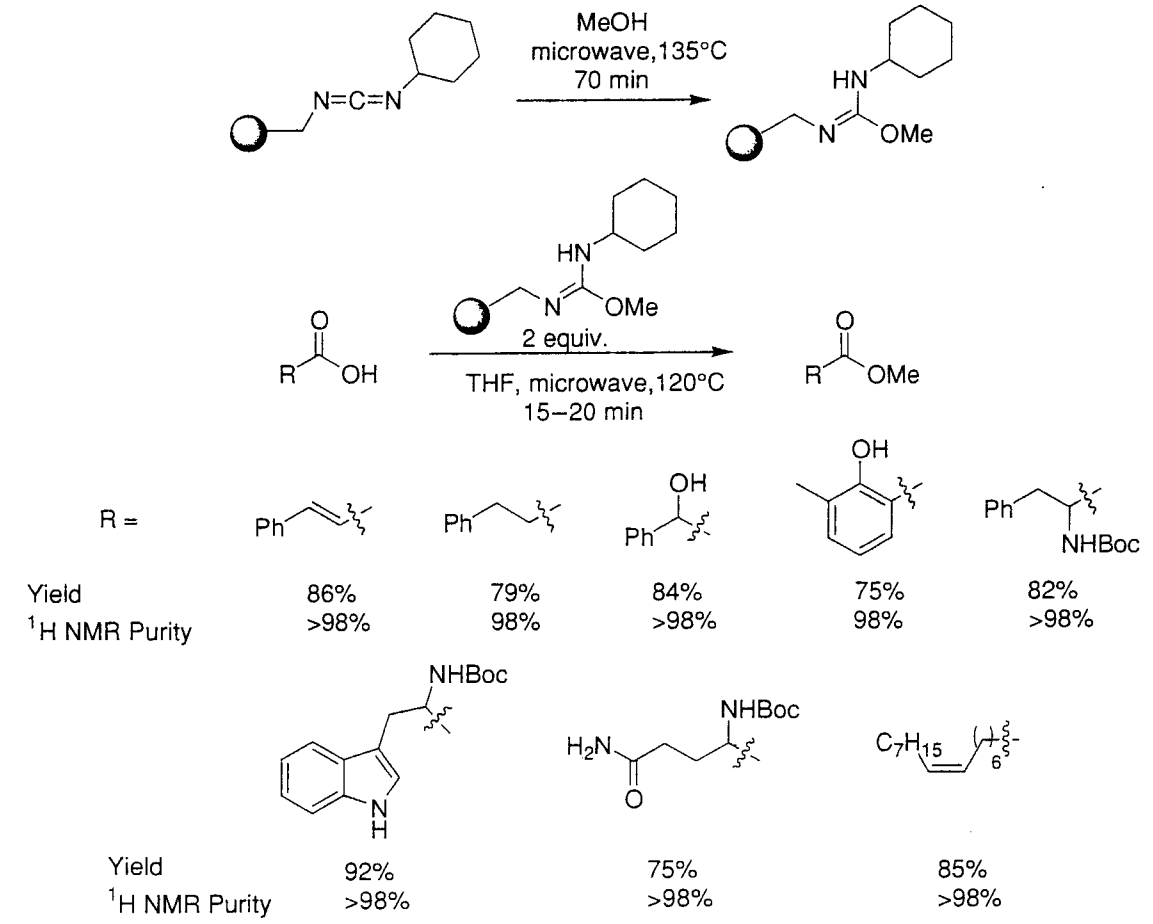


Figure 6.4 Comparison of heating profiles associated with microwave and traditional conductive heating methods.

(Scheme 6.5)[133,134]. In the initial work using this reagent, an overnight reflux (16–20 h) in THF was required to achieve comparable conversions. As previously mentioned, the shorter reaction times provided by this approach are certainly more compatible with the use of resin-type supports. The authors make the comment that under the optimised reaction conditions they identified no significant degradation of the polymer. It was also reported that the acceleration of the reaction did not affect the chemoselectivity of

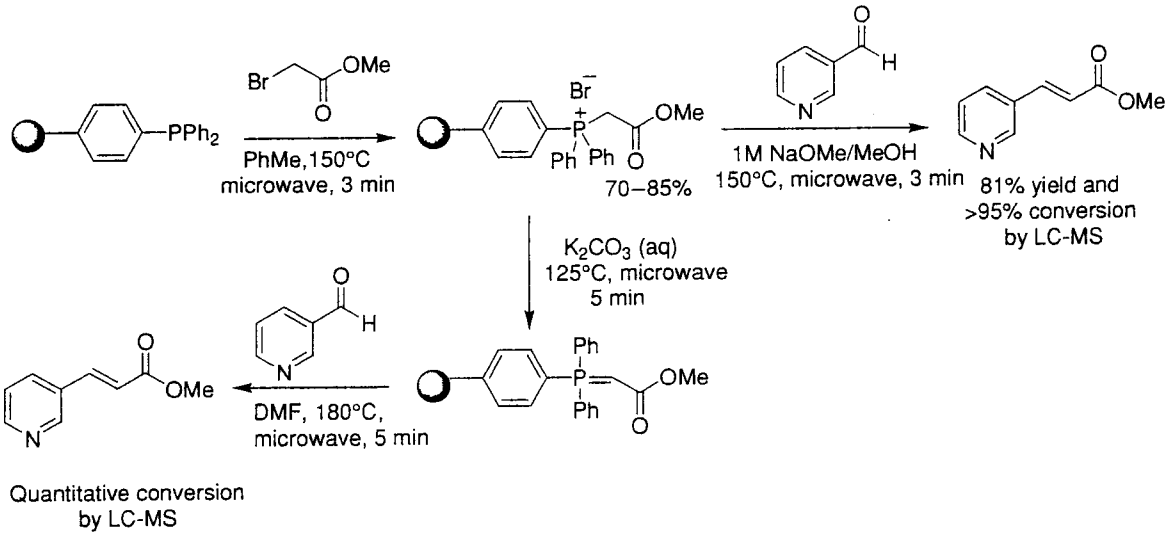


Scheme 6.5

the reagent, with alcohols, phenols and primary amines remaining inert. Besides conducting the esterification reactions under microwave heating, the polymer-supported *O*-methylisourea reagent was itself formed by irradiation of the carbodiimide resin in dry MeOH. In contrast to the initial unsuccessful attempts at making the reagent using traditional copper(I) catalysis, high pressure thermolysis in a focused microwave oven at 135°C for 70 min allowed complete conversion. This approach to the use of microwaves as a primary heating method really highlights the utility and practicality of such techniques in synthesis.

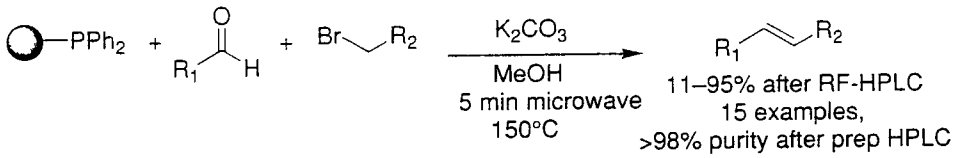
6.3.6. *Wittig reactions*

The Wittig reaction, although of high synthetic value, can often be both time consuming and labour intensive to carry out. Both the initial preparation of the phosphonium salt and the ensuing reaction of the ylid species with a suitably functionalised carbonyl are often slow processes. These difficulties are additionally compounded by the relatively low stability of the Wittig intermediates, which often prevent the use of elevated reaction temperatures especially over extended periods of time. Finally, on completion of the reaction, purification can also be troublesome because of problems encountered with the separation of the product from contaminating triphenylphosphine oxide. It would, therefore, be highly advantageous if a method could be found to circumvent these problems. A recent report proposes to have achieved this through the combined use of an immobilised triphenylphosphine equivalent and rapid microwave heating[135]. The initial development phase of the research was directed at procedures for accelerating the three individual steps of the reaction, by employing short but intense microwave heating sequences (Scheme 6.6). This approach proved highly beneficial for shortening the reaction times and simplifying the work-up procedure without jeopardising the yields or purities of the products.



Scheme 6.6

In an extension of this work, the authors devised a more convenient one-pot procedure where all reaction components were heated simultaneously using microwave irradiation (Scheme 6.7). This protocol allowed the generation of a small set of ten compounds in poor to excellent isolated yield following preparative HPLC. This method certainly constitutes a very significant result, especially considering its applicability to high throughput combinatorial synthesis.



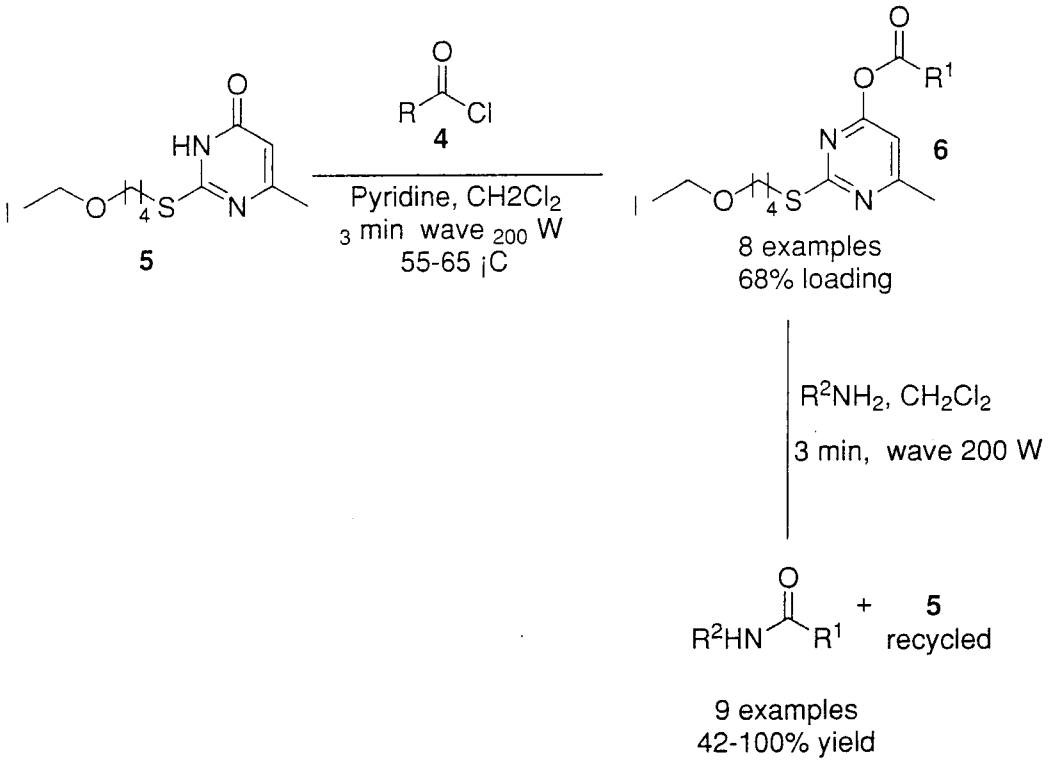
Scheme 6.7

6.3.7. *Acylation reactions*

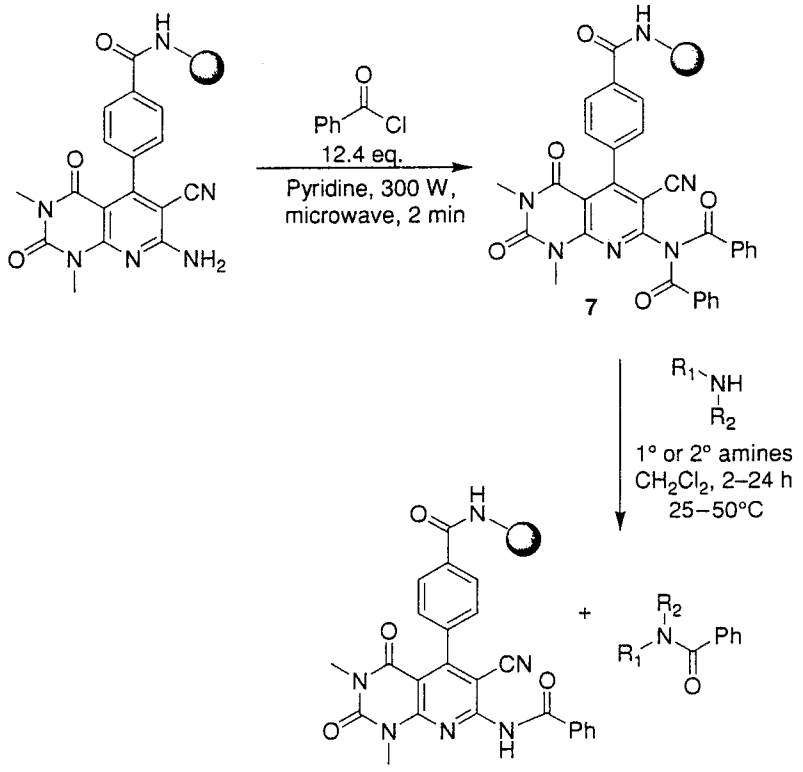
The acylation of various functional groups is one of the most fundamental chemical manipulations in organic chemistry. This is particularly important when the formation of amide bonds are considered, as exemplified by the prevalence of the peptide bond within nature. Accordingly, there are numerous synthetic methods and reagents dedicated to the activation and coupling of these units. Unfortunately, many of the reagents and additives used in these reactions can be difficult to remove or display high toxicity. To simplify the isolation procedure and increase the safety profile, a number of these reagents have been immobilised on solid supports. It has been demonstrated that at least two of these reagent systems display shortened reaction times and improved yields when integrated with a microwave heating procedure[136,137].

Botta *et al.* have applied microwave heating procedures to both the preparation of their immobilised reagents and also to facilitate its subsequent reactions (Scheme 6.8)[137]. The initial preparation of the acylating reagents was carried out using 4 equiv. of the acid chloride **4** in a mixture of pyridine and dichloromethane with irradiation for 3 min at 200 W. The immobilised 4-acyloxypyrimidine **6** was then progressed through a washing sequence, resulting in a resin with approximately 68% of its potential theoretical loading. This activated material could then be suspended in dichloromethane with the required amine and irradiated for 3 min, again at 200 W. A rapid filtration and evaporation of the solvent provided the amide products as crystalline solids in good to excellent yield. The spent resin **5** from these reactions could be easily recycled for several runs without any detectable loss of activity.

In a similar way, Nicewonger and co-workers used microwave-mediated conditions to prepare a solid-phase imide **7** as an amine acylating reagent (Scheme 6.9)[136]. As in the above example, the spent resin could be easily isolated, washed and reactivated for further acylation cycles by repeating the microwave activation sequence. Using this reagent, excellent yields were obtained with both primary and secondary derivatives, but no reaction was observed with anilines. It is surprising that despite the emphasis the authors put on the ability of microwave heating to drive normally sluggish reactions to



Scheme 6.8



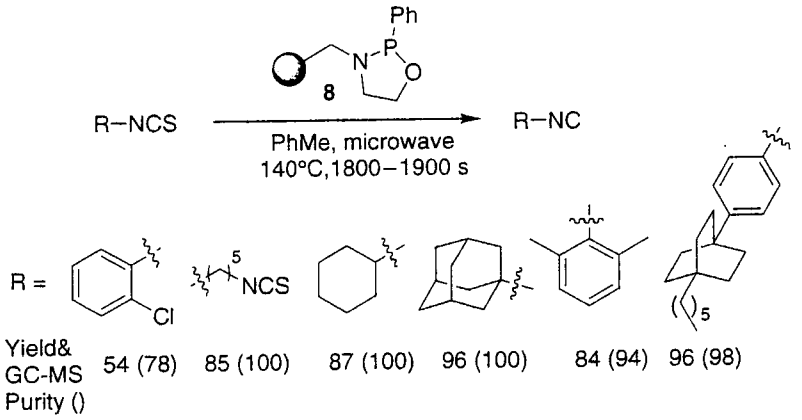
Scheme 6.9

completion, no reported attempt was made to apply this concept to the reaction of the anilines, with only temperatures of 25–50°C at atmospheric pressure being applied.

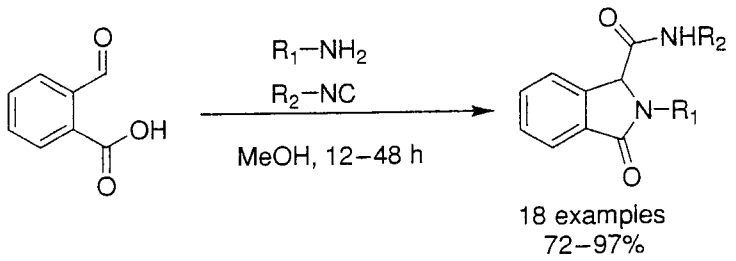
6.3.8. *Preparation of isocyanides*

The availability of novel monomer building blocks has become an important consideration in combinatorial chemistry because of the greater emphasis placed on diversity and novelty in modern library generation. Isocyanides have received particular attention because of their unique reactivity in multi-component coupling reactions, such as the Passerini[138] and Ugi[139,140] reactions. To augment the commercial supplies of these compounds, a number of groups have devised short and efficient protocols for their generation[141–145]. Unfortunately, the isolation of the isonitrile products can be problematic due to their high reactivity and in certain cases instability to traditional forms of extraction and purification. To overcome these difficulties, two independent approaches have been devised that combine the easy work-up protocols allowed by immobilised reagents and the rapid and efficient conversions attained by using flash microwave heating.

The first of these methods involves the *in situ* generation of isocyanides from the corresponding isothiocyanates using a supported [1.3.2] oxazaphospholidine species **8** (Scheme 6.10)[146]. This clean and efficient reagent was successfully used to generate, on demand and in parallel, a wide selection of isocyanide products. These materials were then submitted to an Ugi coupling reaction to prepare a focussed library of bicylic amides (Scheme 6.11).



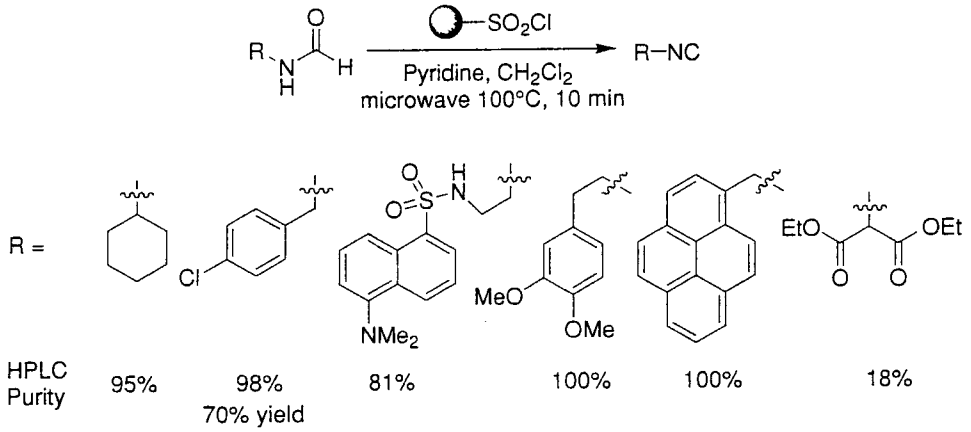
Scheme 6.10



Scheme 6.11

Interestingly, the same reagent was also used in the conversion of isothiocyanates to isocyanides under conventional thermal conditions. Whilst isocyanides were successfully produced, the products were discovered to be highly susceptible to a competing rearrangement process, generating the equivalent nitriles after prolonged heating[147].

The second preparative procedure was used to transform formamides to isocyanides with an immobilised sulphonyl chloride (Scheme 6.12)[148]. The reactions were performed rapidly (ca. 10 min) under microwave heating (100°C), in the presence of excess pyridine to give the corresponding isocyanide in high overall purity, although in only modest yield. The only yield quoted in the paper is 70%, although independent attempts on other substrates have given similar results. The procedure described does, however, avoid the tedious requirement for chromatographic purification that was necessary in the original solution-phase procedure, although it still requires an aqueous extraction sequence to afford clean products. An important point to note is that the spent resin could be quantitatively regenerated by treatment with 5 equiv. of phosphorous pentachloride (PCl_5) in dichloromethane at ambient temperature. Although this is a very effective method, it is not always a simple process to remove the phosphorous by-products from the resin, which can result in contamination in subsequent reactions.



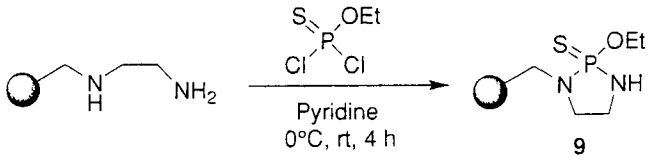
Scheme 6.12

6.3.9. *Synthesis of thioamides*

Thioamides are synthetically versatile molecules being key components in the preparation of many useful heterocycles. The traditional synthetic approaches to the generation of thioamides usually require rather harsh conditions, long reaction times and often result in difficult product isolation procedures. Moreover, the reagents and by-products associated with their synthesis can possess strong malodour and extremely high toxicity, making scale up or high throughput synthetic application technically very challenging.

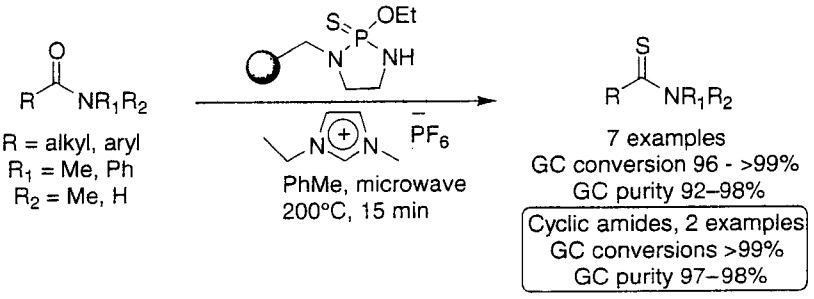
Recognition of these drawbacks prompted the Ley group to design a new polymer-supported reagent **9** for direct amide thionation[149]. Preparation of this immobilised

reagent was very simple and has been conducted on a relatively large scale (150 g of resin) (Scheme 6.13).



Scheme 6.13

This novel reagent cleanly converted both 2° and 3° amides into their corresponding thioamides under conventional thermal conditions (90°C, 30 h). However, the microwave-induced transformation was significantly faster. Heating the reactions in a sealed reaction vessel at 200°C for 15 min furnished the desired thioamides in almost quantitative yields with no purification step necessary apart from filtration of the resin (Scheme 6.14). These optimised conditions were obtained by conducting the reactions in a mixture of toluene and the ionic liquid 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate (20:1). This was found to be an excellent compromise between the requirements for the non-polar solvating properties of toluene for effective swelling of the resin and the necessity for a strong dipole to aid dielectric heating. To our knowledge, this represents the first reported application of an ionic liquid for increasing the thermal profile of a solution under microwave irradiation. For the same reason, acetonitrile, a strong dielectric heater, was also investigated as an alternative dopant, but proved to be less efficient than the ionic liquid. Under these conditions, treatment of 1° amides with the immobilised reagent led only to the corresponding nitrile – an observation that was consistent with results published for the solution-phase reaction of 1° amides with Lawesson's reagent[150].



Scheme 6.14

Further studies have shown that the same reagent species can be effectively constructed on a silica backbone giving appreciable increased reactivity[151] (S.V. Ley, unpublished results). A silica-based support provides advantages in terms of more effective heating profiles because of the superior absorbency of the silica and increased compatibility with

a wider range of solvents. By using these supplementary attributes it has been possible to process a wider variety of substrates, thus increasing the synthetic utility of this reagent.

6.3.10. *Esterification of alcohols using heterogeneous acid catalyst*

Kabza and co-workers have investigated the kinetics of the simple Fischer-type esterification of isopentyl alcohol and acetic acid using a heterogeneous polymer-supported reagent[152,153]. Amberlyst 15 sulphonic acid resin was used as a strong protic acid catalyst under microwave heating conditions to search for evidence of athermal effects, derived from the selective superheating of the immobilised catalytic sites during the transformation. A continuous-flow reactor as depicted in Fig. 6.5 was constructed to facilitate rapid and continuous monitoring of the reaction, while various experimental parameters were altered. From their findings, they concluded that the reaction investigated behaves analogously under both microwave-mediated and classically heated conditions. The reaction kinetics demonstrated no 'energy-type' preference or specific rate enhancements when microwave heating was applied. The authors report an additional interesting discovery, in that increasing the proportion of water present in the resin significantly retarded the reaction rate. In fact, the rate constant for the reaction was similar to that reported for the equivalent reaction carried out under fully aqueous conditions[153]. The experimental data obtained in the study suggested this effect was not purely due to an alteration of the equilibrium constant as a result of the additional water content, although this was making the assumption that the system behaves like an

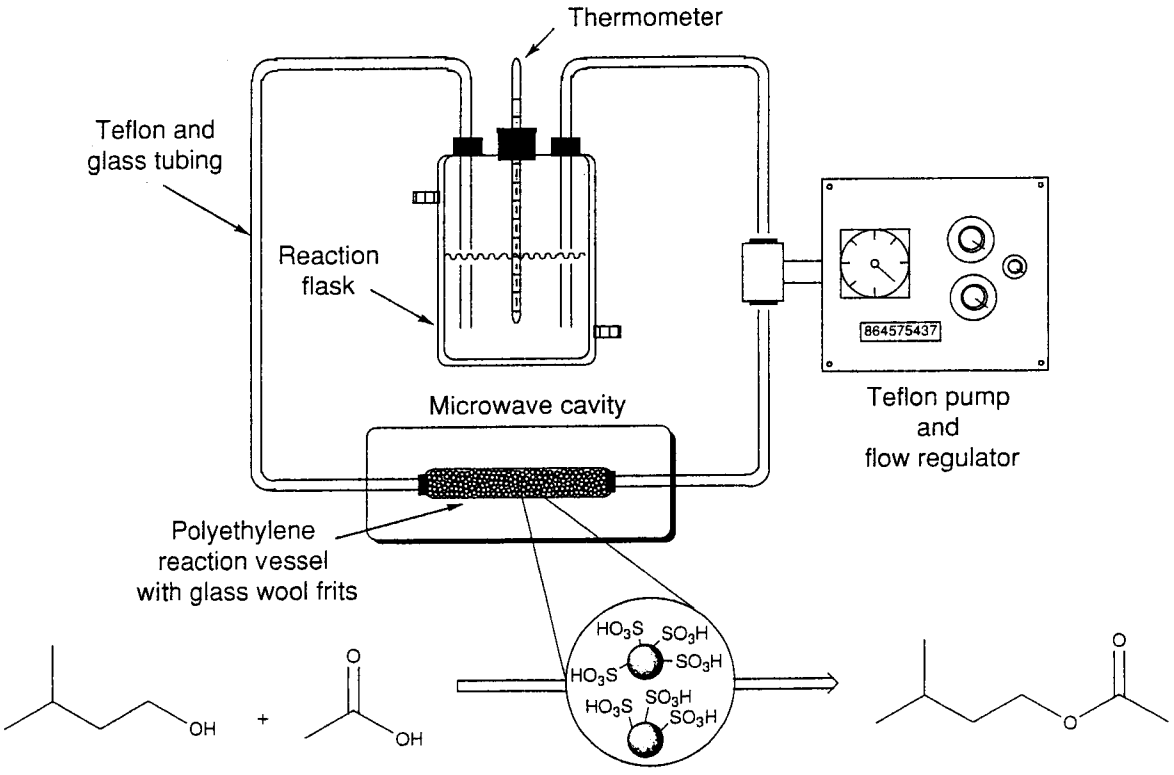
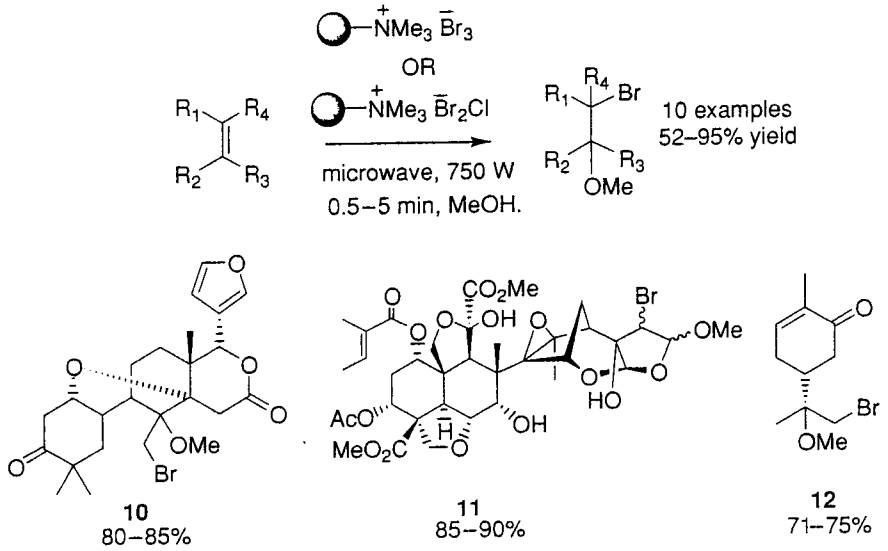


Figure 6.5 Fisher esterification reaction using a continuous batch flow reactor.

ideal homogeneous reaction. Kabza proposed that this observed aqueous impediment was actually as a consequence of trapped water within the porous cavities of the resin reducing accessibility to the catalytic sites[154]. This work represents only a preliminary study of this type of system and as the authors are quick to point out, a more detailed and better understanding of heterogeneous environments is still required.

6.3.11. *Chemoselective bromomethoxylation*

The selective bromomethoxylation of a variety of alkenes under microwave irradiation conditions have been demonstrated using two polymer-supported macro-porous bromine resins. The reactions have been easily achieved in moderate to good yields and high regio-and chemoselectivity (Scheme 6.15)[155]. All the experiments were carried out in a modified domestic microwave oven fitted with a standard reflux condenser. Reactions were complete within a range of 30 s to 5 min when methanol was used as the solvent. Ten different compounds were reported, including a number of sensitive natural product derivatives such as methyl angolensate derivative **10**, azadirachtin-A derivative **11** and carvone derivative **12**. It is quite remarkable that molecules containing such sensitive functionality as azadirachtin-A can survive these conditions, although we too have noticed the benefits of using microwave heating in connection with this molecule[28]. Unfortunately, no comparison was made with a conventionally heated reaction at the equivalent temperature, or any indication of the length of time such reactions required under ambient conditions.

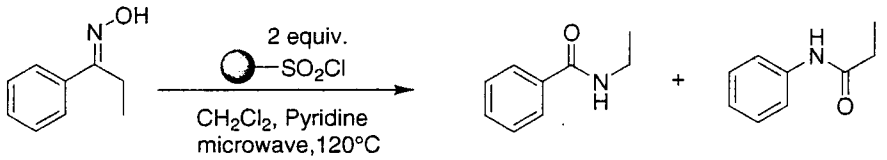


Scheme 6.15

6.3.12. *Beckmann rearrangement*

Another transformation that has received considerable interest is the Beckmann rearrangement. Traditionally, this process requires the presence of a strong acid with heating at high temperatures over extended periods of times. It therefore represents an

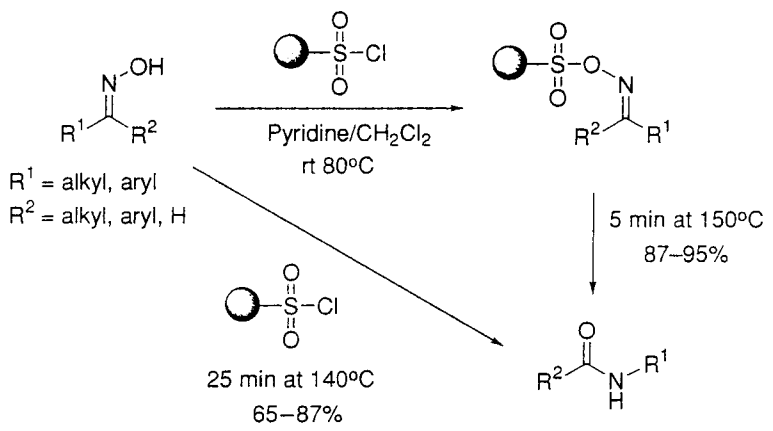
ideal candidate for the application of microwave flash heating. Recently, a number of publications have shown that the reaction can be accelerated using microwave-assisted heating, when conducted under solvent-free conditions using mineral clays as acidic supports[18,156]. Although a very valuable addition to the repertoire of available transformations, this approach is rather limited in its versatility. For example, this approach precludes the ability to intercept the transient intermediates, which would otherwise allow propagation of alternative reaction pathways. The reaction can, however, be carried out in solution employing a sulphonyl chloride resin as the oxime activator. Brown and colleagues have demonstrated that a standard Beckmann rearrangement can be promoted using this immobilised reagent, and further more, the selectivity of the migration can be affected by the specific conditions employed (Scheme 6.16) (R.M. Hughes and R.C.D. Brown, unpublished results; I.R. Baxendale and S.V. Ley, unpublished results).



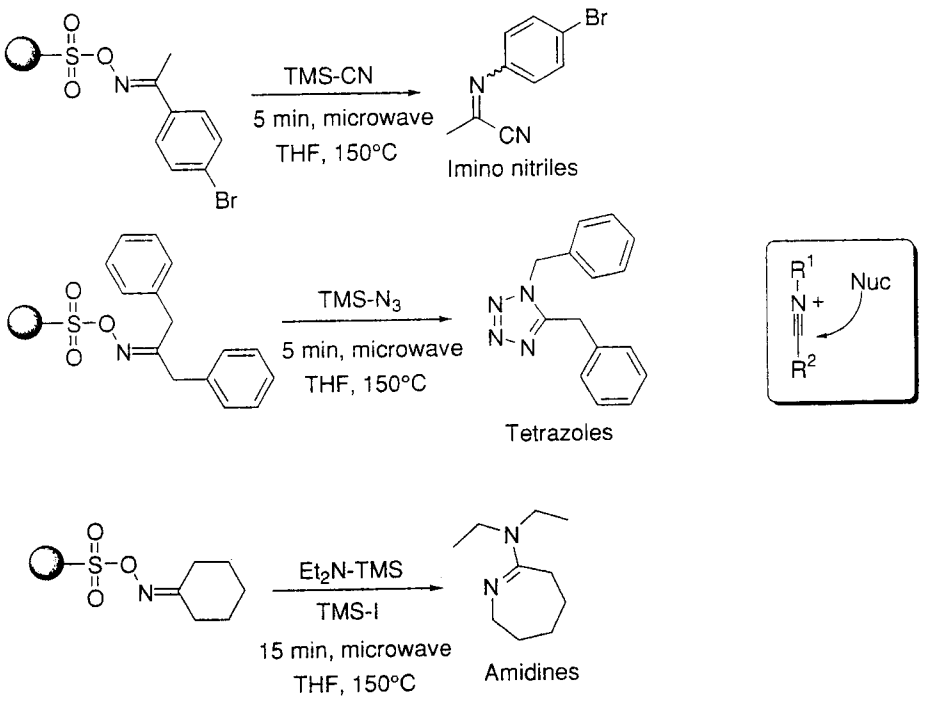
rt 20 h	30%	0%
microwave 10 min	42%	0%
microwave H_2O (3 equiv.) 20 min	40%	8%

Scheme 6.16

The Ley group were simultaneously involved in a more diverse investigation of this reaction[151] (S.V. Ley, unpublished results). They have shown that it is possible to directly transform the oximes to the corresponding amides, by simply mixing with sulphonyl chloride resin and irradiating the resulting suspension (Scheme 6.17). They also demonstrated that the reactive intermediates can be trapped with a number of nucleophilic components to gain access to valuable heterocyclic products and other useful intermediates (Scheme 6.18). Further research to fully exploit this approach, including the expansion of the range of nucleophiles, is currently underway.



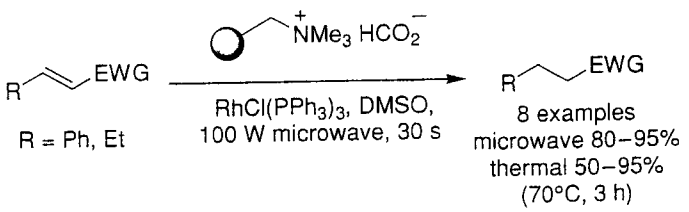
Scheme 6.17



Scheme 6.18

6.3.13. *Hydrogenation of electron-deficient alkenes*

Catalytic transfer hydrogenation is a crucial reaction in organic synthesis. Most applications of this reaction employ ammonium formate as a hydrogen source in the presence of a catalyst, such as palladium charcoal (Pd/C) or Wilkinson's catalyst $RhCl(PPh_3)_3$. However, there are a number of difficulties associated with the use of ammonium formate, such as its ability to sublime, which leads to blocking of the reaction apparatus. In addition, the reaction can generate significant quantities of ammonia, which is problematic when working on a large scale. In an attempt to overcome these problems, Desai and Danks (see Chapter 4) have reported on the use of a polymer-supported formate (on Amberlite IRA 938) for the reduction of electron-deficient alkenes in the presence of Wilkinson's catalyst (Scheme 6.19)[157]. Once again, in comparison to non-microwave conditions, dielectric heating offered a tremendous rate enhancement and increased product purity. It is worth making the general observation that many reactions involving metal catalysts show enhanced substrate reactivity and higher turnover numbers, when employed in conjunction with microwave irradiation. The involvement



Scheme 6.19

of selective superheating of the metal particles combined with temperature-mediated self-cleaning mechanisms (decoking) certainly contributes to these observed benefits.

6.3.14. *Heck reactions*

The development of novel supports and presentation formats has become an important consideration in solid-phase chemistry, particularly in the area of immobilised catalysts. The ability to bind transition metals such as palladium to the surface of an extractable solid support facilitates rapid and convenient recycling. It has also become apparent that certain immobilised metal species can gain significantly enhanced reactivity from selective heating mechanisms produced by microwave energy transfer. Buchmeiser and co-workers have prepared two alternative supports based on ring-opening metathesis polymerisation (ROMP) grafting techniques. These macromolecular structures contain ligating sites, which have been used to immobilise palladium dichloride to create catalysts for use in Heck type reactions (Fig. 6.6)[158].

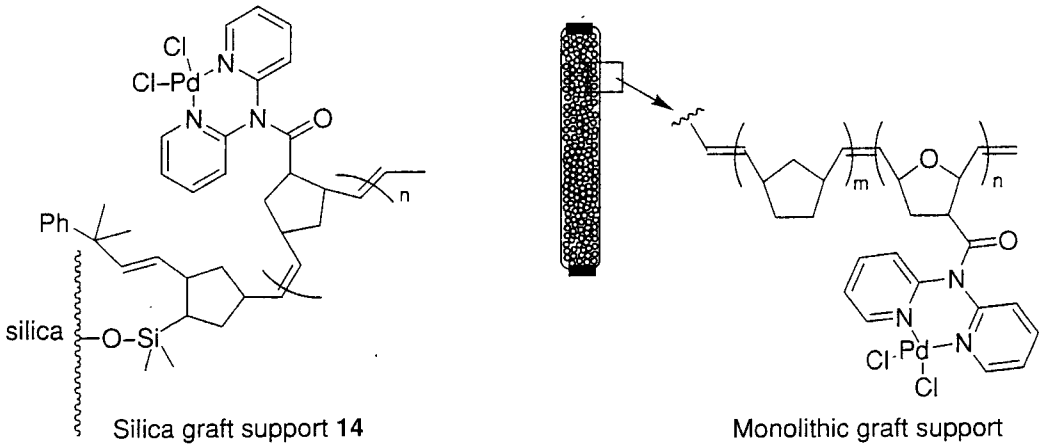
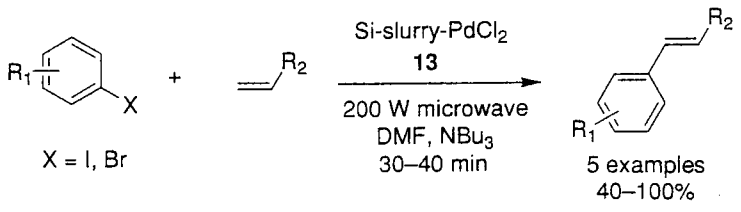


Figure 6.6 (a) A silica immobilised palladium catalyst for Heck reactions. (b) The same catalyst prepared in a Monolithic graft support.

Slurries of the silica-based material **13** were used for Heck coupling of aryl halides and styrene-based alkenes under standard as well as microwave heating conditions (Scheme 6.20). Microwave irradiation leads to drastic reductions in the reaction times, proving, on average, to be six times faster. The supports also displayed very low levels of leaching, typically <2.5%, although it was not clear from the paper if this was affected by the method of heating. Interestingly, the silica support **14** and the monolithic

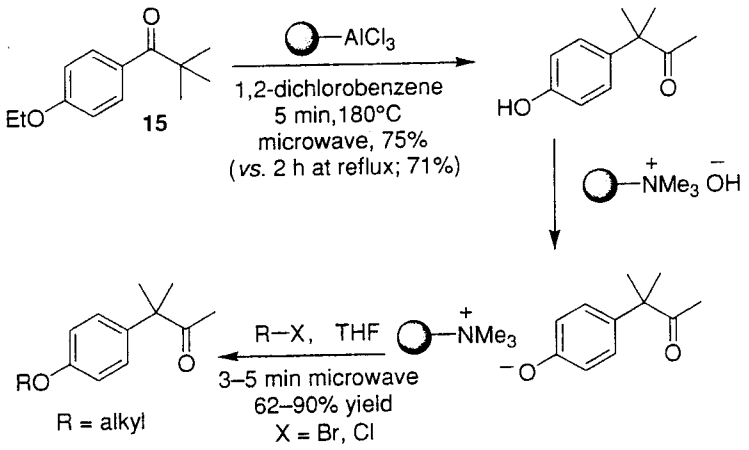


Scheme 6.20

material displayed in Fig. 6.6 could be packed into column cartridges and used in a continuous flow process. In these systems, only traditional heating methods were attempted, although the design of reactors to facilitate microwave irradiation of such systems has already been proven (see Chapter 9), so additional work on this area will not be long in coming.

6.3.15. *Ketone–ketone rearrangements using polymer-supported $AlCl_3$*

A recent publication from an Indian group has described the synthesis of a small selection of 3-(4-alkoxyphenyl)-3-methylbutan-2-ones, which are useful starting materials in the synthesis of a wide range of natural products. A polymer-supported aluminium chloride species[159] was used to catalyse the rearrangement of ketone **15**, followed by O-alkylation of the trapped intermediate with simple alkyl halides (bromo and chloro) as well as dimethyl and diethyl sulphate (Scheme 6.21)[160]. Both transformations were found to occur with improved efficiency, when the heating was conducted using microwave irradiation. The authors claim this procedure is the simplest and most economical methodology used to synthesise these intermediates to date.

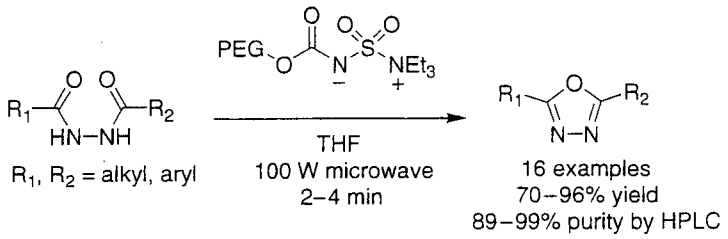


Scheme 6.21

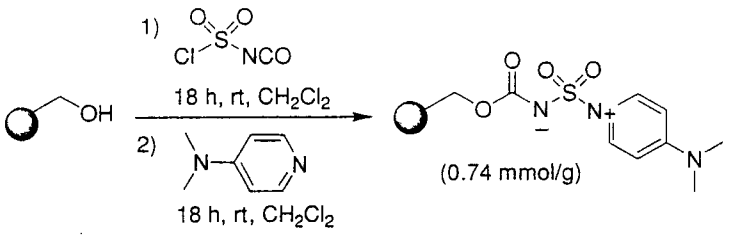
6.3.16. *Synthesis of 1,3,4-oxadiazoles using polymer-supported Burgess reagent*

On the basis of a wealth of information concerning the dehydrating properties of the solution-phase Burgess reagent, Brain and co-workers at Novartis have demonstrated that the analogous polymer-supported equivalent, first synthesised by Wipf[161], could be ameliorated when used in conjunction with microwave heating protocols (see Chapter 3)[162,163]. In this way, they were able to facilitate the swift cyclo-dehydration of 1,2-diacylhydrazines to the corresponding oxadiazoles (Scheme 6.22). These products were easily isolated in high overall yield and purity by a simple filtration through a frit of silica gel to remove the PEG-supported materials.

Although this protocol was very mild and efficient, the methodology was subsequently revised by the generation of a new heterogeneous polystyrene immobilised

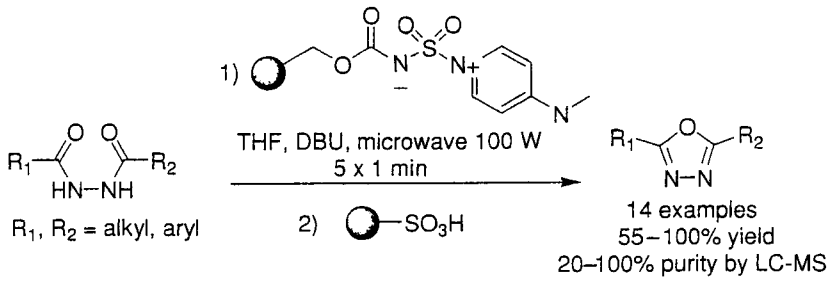


Scheme 6.22



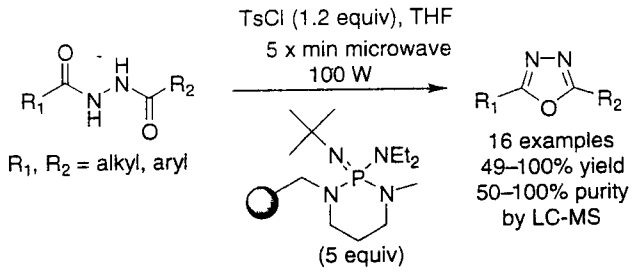
Scheme 6.23

variant of the Burgess reagent (Scheme 6.23)[162]. The synthesis of this modified material alleviated the need for a silica gel purification step, and in addition, aided the recovery and recycling of the spent resin. It also demonstrated good stability and could be stored for over a month when refrigerated under a nitrogen atmosphere, although it could be conveniently handled in air during dispensing. Initial experiments employing this species have been successful, affording relatively high yields of the heterocyclic product. However, a further improvement was achieved with the introduction of the strongly basic guanidine additive DBU. Using the optimised reaction conditions, a rapid and near quantitative formation of 14 structurally diverse oxadiazoles was achieved. Reaction clean up was achieved using an immobilised sulphonic acid (Amberlyst 15), which was added directly to the crude reaction mixture to expediate the removal of the excess guanidine base. A single filtration step followed by evaporation of the solvent yielded the heterocyclic products (Scheme 6.24). Throughout this work traditional thermal heating was conducted in parallel with the microwave experiments, although in the majority of cases this resulted in substantially lower yields and purities, along with the requirement for prolonged reaction times.



Scheme 6.24

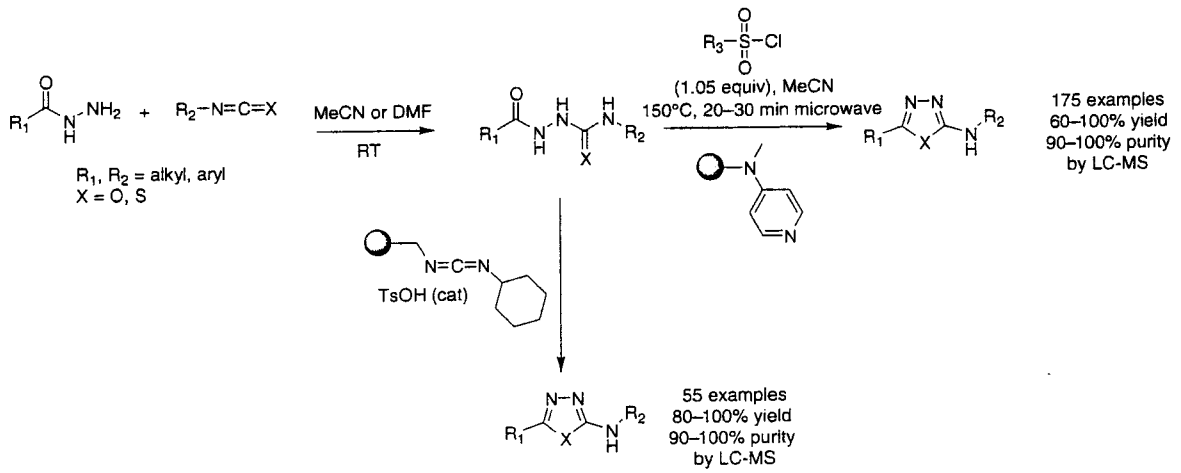
In the same publication, it was reported that this cyclo-dehydration could also be affected by using tosyl chloride and the polymer-supported phosphazene base PS-BEMP, and again, microwave heating was found to be advantageous (Scheme 6.25). In utilising this protocol, no scavenger purification strategy was deemed necessary and the authors note that this is the most efficient 1,3,4-oxadiazole synthesis of the three polymer-supported methods described.



Scheme 6.25

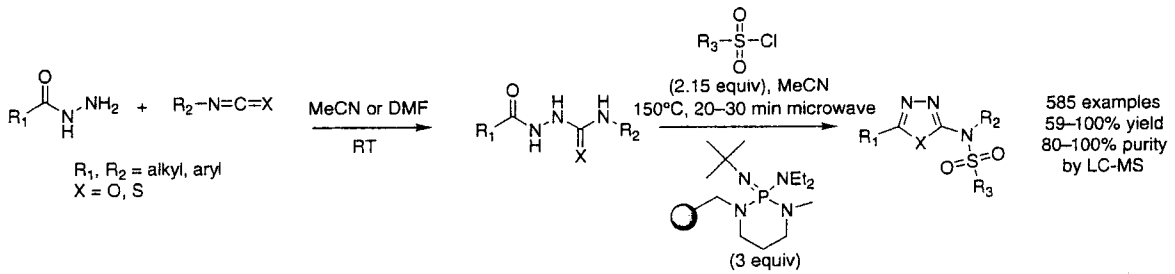
6.3.17. *Preparation of a substituted 2-amino-1,3,4-oxadiazole library*

A related series of 5-substituted-2-amino-oxadiazole compounds have also been prepared in a one-pot procedure using a microwave-assisted cyclisation procedure (Scheme 6.26)[164]. Rapid preparation of the pre-requisite ureas from the mono acyl hydrazines and various isocyanates (or the isothiocyanate) was easily achieved by simple mixing. The resulting products were then cyclodehydrated by one of the two procedures: either by the addition of polymer-supported DMAP and tosyl chloride or alternatively with an immobilised carbodiimide and catalytic sulphonic acid. Purity in most cases was excellent after only filtration through a small plug of silica but an SCX-2 cartridge (sulphonic acid functionalised – catch and release) could be used in the cases where reactions required additional purification.



Scheme 6.26

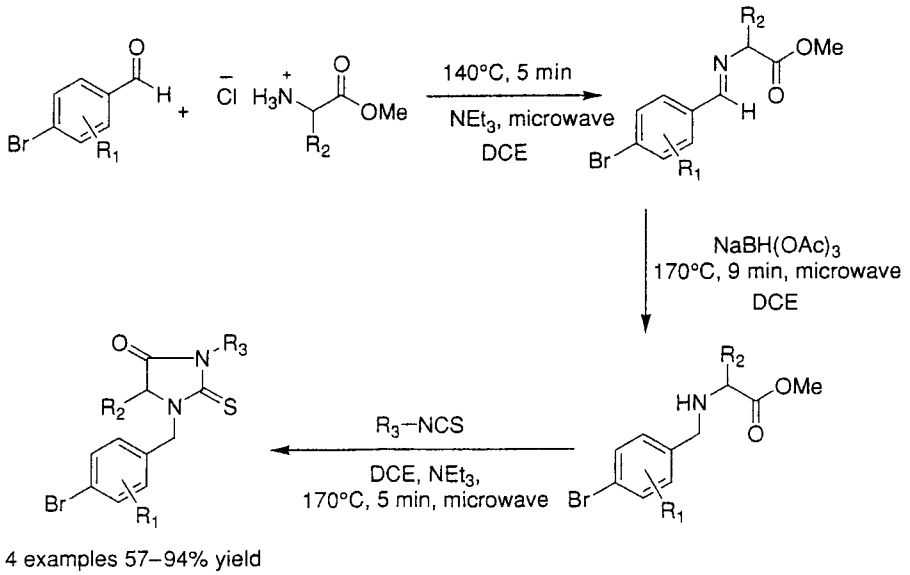
As an extension of this work Ley *et al.* demonstrated that it is possible to prepare the corresponding *N*-protected sulphonamides in an analogues single-pot procedure (Scheme 6.27). The addition of a 2.1 equiv. excess of a sulphonyl chloride to the urea in the presence of the stronger immobilised base PS-BEMP facilitates both the cyclisation and subsequent sulphonylation steps. The isolated products following filtration were obtained in both high yields and excellent purities although certain reagent combinations resulted in the formation of the alternative regioisomer as a major product. It was noted that the solvent played an important role in the generation of the regioisomeric structures with changes in mixture compositions of 35:1 to 1:1 being observed when swopping from MeCN to THF. Additional investigations are under way to further understand and exploit these findings.



Scheme 6.27

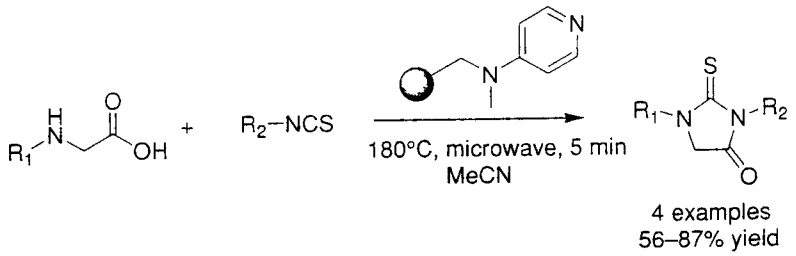
6.3.18. *Synthesis of thiohydantoins*

In another heterocycle forming procedure, Westman *et al.* (see Chapter 5) employed microwave dielectric heating to a sequential one-pot, three-step reaction sequence leading to an array of structurally diverse thiohydantoins (Scheme 6.28)[165]. Although the final sequence is a purely solution-phase protocol, involving no immobilised reagents,



Scheme 6.28

the authors do describe their initial investigations, which involved the direct coupling and cyclisation of amino acids with isothiocyanates, catalysed by a polymer-supported DMAP reagent (Scheme 6.29). They state that this method provided a much cleaner reaction mixture when compared with the final solution-phase step, which uses triethylamine; however, this supported reagent step was unfortunately less compatible with the other steps of the synthesis.



Scheme 6.29

6.3.19. *Hydrolysis of sucrose to fructose*

The hydrolysis of sucrose to form fructose and glucose, catalysed by the strongly acidic cation-exchange resins Doulite C25D[166] and Amberlite 200C (protic forms)[167–169], has also been studied. The principle work by Wang and co-workers[166] used a modified domestic microwave oven containing a Teflon coil as a readily adaptable continuous flow reactor. The coil situated within the microwave cavity (ca.10 ml in volume) was packed with the immobilised Doulite particles and a solution of sucrose was slowly pumped through the system. The reaction required only a 10 min residence time at 72 W to achieve a 95% conversion. Of significant interest is the observation that the use of the strongly acidic Doulite C25D resin gave better results than comparable experiments with a mineral acid. More recently, Plazl[167–169] has investigated the same reaction under both conventional and microwave heating with a view to analyse the response of the reaction to changes in the heating mechanism. Initial reactions were conducted in a stirred tank reactor, which was housed in the chamber of a domestic microwave oven. Later a more sophisticated fixed bed reactor was constructed. In this set up the immobilised catalyst (Amberlite 200C) was located in a Pyrex glass tube sited in the microwave cavity (Fig. 6.7). Automated on-line monitoring of the various fluid inputs and outputs allowed a detailed analysis and the development of a mathematical model to predict the heating requirements and thermal profile of the reactor. In this way, it was possible for the researchers to optimise the power settings, flow rates and temperature requirements in order to produce a given conversion of the sucrose or successfully predict a given level of transformation from a set of experimental parameters.

6.3.20. *Microwave-promoted enzymatic reactions*

The use of enzymes as reagents in general organic synthesis is becoming more widespread as the scope of the transformations for which they can be applied is more thoroughly investigated and understood. The thermal acceleration of enzymatic transformations

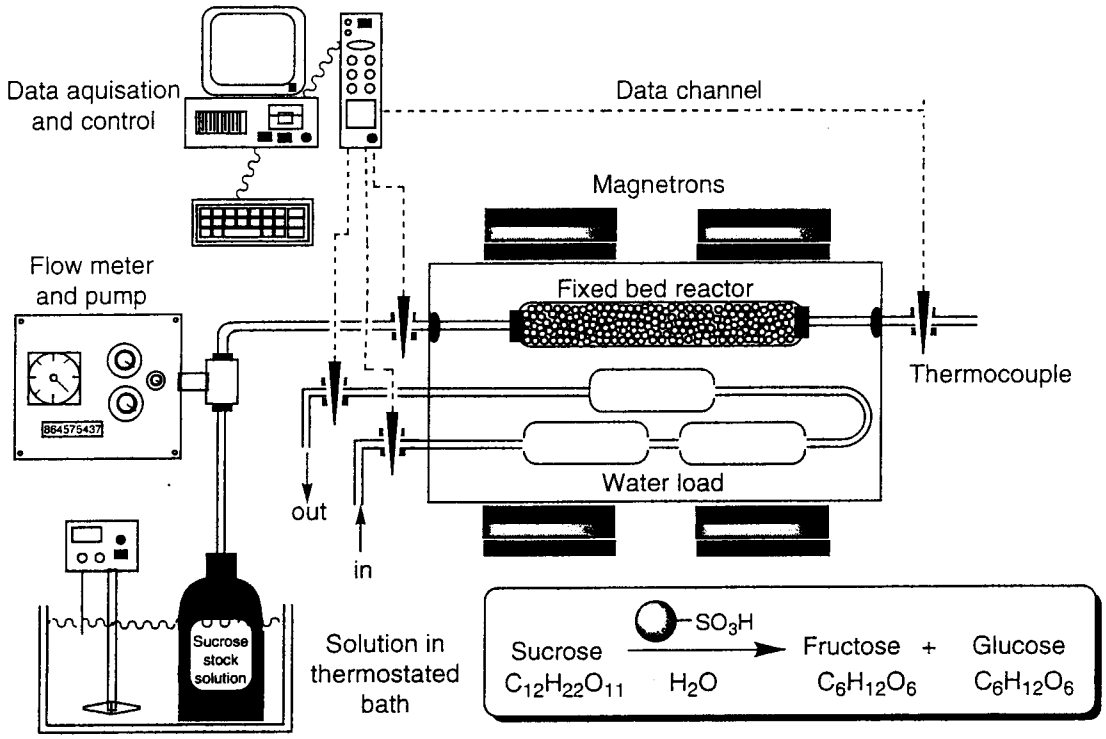
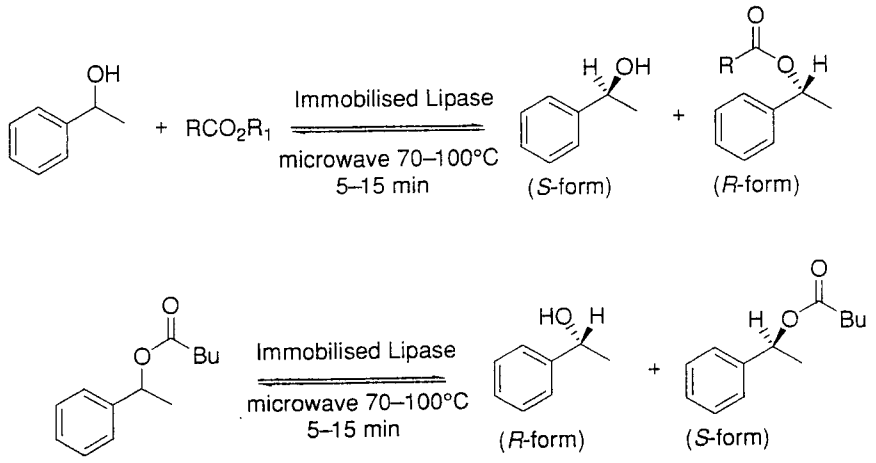


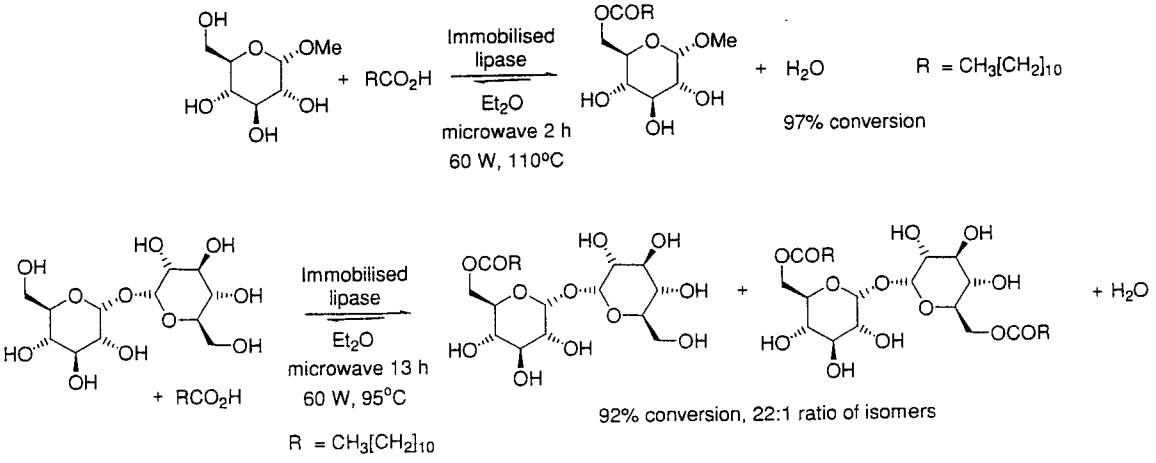
Figure 6.7 A diagrammatic representation of a fixed bed reactor used for the degradation of sucrose.

is generally perceived to reduce the enantiospecificity of the process. However, a growing population of literature indicates that many biological catalysts are not as strictly temperature dependant as previously assumed[170–173]. In addition, the further use of designer thermostable enzymes prepared by recombinant DNA technology now permits regular application of enzymes at relatively high temperatures[174]. Loupy *et al.* have identified the potential gains to be leveraged by using microwave heating in combination with enzymatic processes[175,176]. Their approach relies on the ability to induce equilibrium shifts in the composition of the biological mixture, by evaporation of low-molecular-weight polar molecules. This is achieved by selective excitation of the small molecule fractions as a result of their strong coupling interaction with the microwave irradiation. In their original work, they investigated the lipase-catalysed resolution of 1-phenylethanol under 'dry'/solvent-free conditions, with the enzymes immobilised on a solid support (various supports were tested including Accurel a polypropylene resin) (Scheme 6.30). The working temperatures for the investigated esterification and transesterfication reactions were in the range of 70–100°C; this was achieved using a single-mode microwave reactor with a controllable power setting for maintaining the temperature. The reactions showed very pronounced increases in their general rate of acyl transfer under these conditions, which could be directly related to the exclusion of the volatile by-products from the equilibrium. In this way, it was also possible to demonstrate that normally low-yielding reactions (not fully resolved) could be driven to completion, obviating the need for further enantiomeric separation. In most cases, when compared to classical heating methods, the microwave-promoted reactions gave higher stereoselectivity and improved kinetics, although with essentially identical levels of conversion for a given temperature. The supported enzymes were also preserved under the microwave conditions and could be recycled without loss of activity.



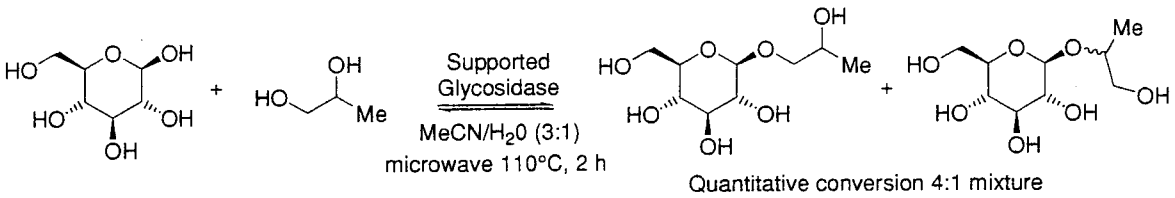
Scheme 6.30

As an extension of their initial work, Loupy and co-workers reported on the regioselective lipase-catalysed esterification of a selection of α-D-glucopyranosides with various fatty acids, under similar microwave-promoted reaction conditions[177]. The lipase *Candida antartica*, immobilised on Novozym 435, was impregnated with the coupling component (fatty acid) and the dried solid material was irradiated with the pyranosides. The comparison with conventional heating conditions at equivalent recorded temperatures and for the same duration of heating showed substantially higher levels of conversion in the cases of microwave heating. For example, the reaction shown in Scheme 6.30 gave >95% conversion after 5 h of microwave heating, whereas the same reaction heated in a thermostatically controlled oil bath was only 55% complete after the same period. Various other sugars were also successfully esterified using this approach, and in all cases the catalysed transformation showed high levels of regioselectivity under microwave conditions (e.g. Scheme 6.31). A probable explanation for this is that the rapid kinetics furnish a high yield of the desired product, which could then be isolated, before any additional equilibria leading to alternatively substituted products were sufficiently established.



Scheme 6.31

In a third paper, the same group continued their studies by evaluating enzymatic glycosidation reactions (Scheme 6.32)[176]. Their general findings were that all the reactions investigated demonstrated enhanced kinetics, when compared to the literature reported analogous transformation. Furthermore, the authors were able to optimise the conditions for transglycosidation reactions resulting in a complete conversion within 3 h while minimising the level of competing hydrolysis – a significant problem that is normally encountered under forcing conditions. It was also found that the proportion of glycoside acceptor could also be significantly reduced to only 2 equiv. Overall, this method of glycosidation represents a very significant improvement over the previous literature examples.



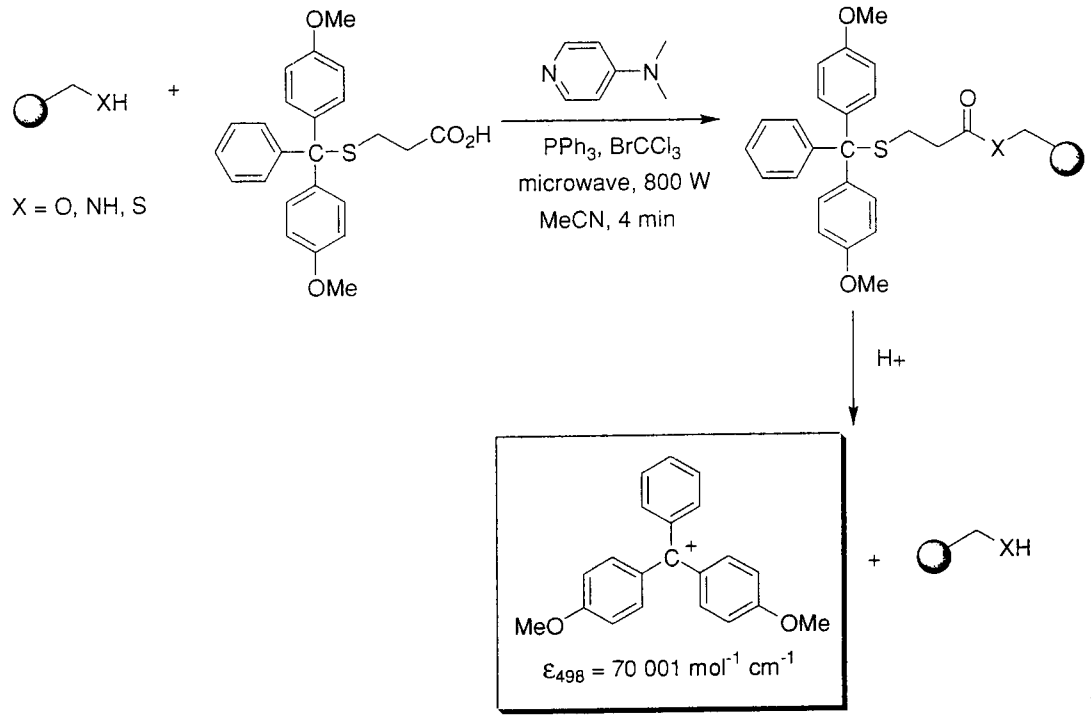
Scheme 6.32

6.3.21. *Spectroscopic estimation of polymer-supported functional groups*

Microwave-assisted heating has also been employed in the determination of polymer-supported functional groups[178]. The reagent (4,4'-dimethoxytrityl)-3-mercaptopropanoic acid (DMPA) in conjunction with a redox coupling mixture of triphenylphosphine and bromotrichloromethane (TTP/BTCM) can be used to assess the total number of assessable hydroxyl, amino or mercapto sites in a given resin. The process is greatly facilitated by the microwave-enhanced coupling of the DMPA to the resin-bound functionality (<4 min). The extent of the coupling can then be estimated in reverse by spectrophotometrically monitoring the levels of dimethoxytrityl cations, which possess a high-molar absorption ($\varepsilon_{498} = 700\,001\ mol^{-1}\ cm^{-1}$), liberated from a known quantity of the resin upon acid treatment (Scheme 6.33). This method has proved advantageous not only for identifying functional group loading on resins for use in solid-phase synthesis, but also for preparing and analysing affinity chromatography matrices.

6.3.22. *The synthesis of (+)-plicamine*

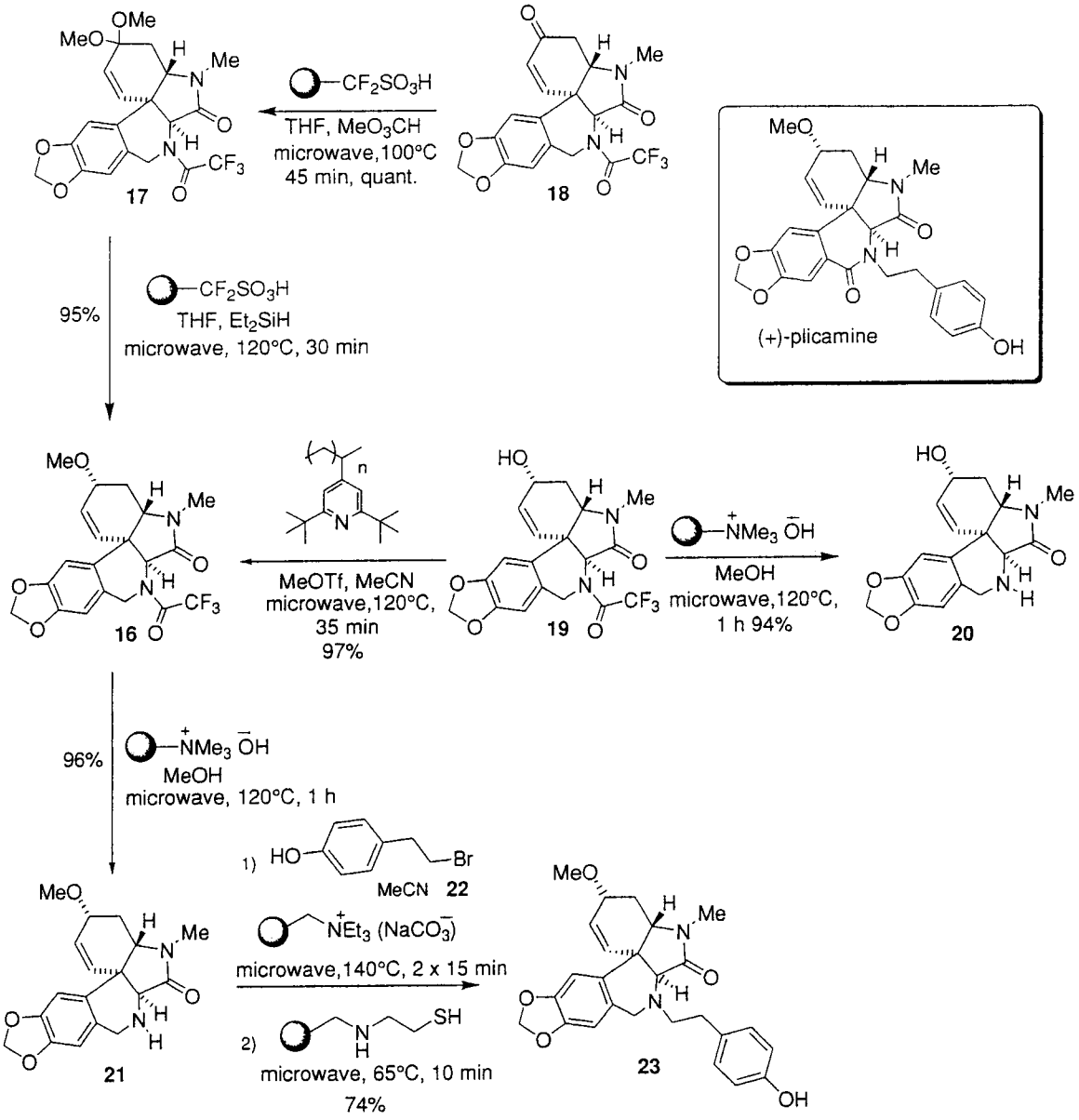
The improved productivity derived through microwave heating in combination with polymer-supported reagents has been used extensively in the total synthesis of the natural product (+)-plicamine as well as a number of related spirocyclic templates[179,180]. Microwave dielectric heating was used as the primary means of accelerating a number of slow reactions, in order to maximise the quantities of intermediates that could be progressed through the synthetic sequence. The rapid optimisation and screening permitted by the adoption of automated microwave reaction handling was crucial to the successful completion of this total synthesis.



Scheme 6.33

Preparation of the key methoxy-substituted intermediate **16** was achieved by one of the two alternative pathways (Scheme 6.34). The initial route involved the reduction of the dimethyl acetal species **17**, which was prepared by microwave heating a mixture of the ketone **18**, trimethyl orthoformate (or dimethoxy acetone) and Nafion SAC-13 in methanol at 100°C for 45 min. This transformation was extremely efficient, giving quantitatively and cleanly the acetal adduct **17** as a crystalline material following only filtration and solvent evaporation. The subsequent reduction step followed a modified procedure from the pioneering work of Olah and co-workers for reductively cleaving acetals using triethylsilane[181]. By conducting the same reaction under microwave heating conditions, the corresponding methyl ether **16** was obtained in an excellent yields, 95% conversion (only yields of 43–56% were obtained following the literature procedure using classical thermal heating). Alternatively, the same material **16** could be synthesised by direct alkylation of the reduced alcohol **19** (*via* reduction with an immobilised borohydride resin), by an activated alkyl donor. The most effective combination of reagents and conditions discovered for this transformation was a blend of methyl trifluorosulphonate and poly(4-vinyl-2,6-*tert*-butylpyridine) under microwave irradiation. Applying normal reflux conditions gave rather disappointing yields as a result of the formation of a diene side-product resulting from elimination of the hydroxyl or methoxy group as a consequence of the prolonged thermal heating (>4 h). This contamination was almost completely avoided with the drastic reduction in heating times permitted when using the microwave system (35 min instead of 8 h).

The cleavage of various trifluoroacetate functionalised amines (e.g. see structures **16** and **19**) has also been accomplished using base-catalysed hydrolysis with Ambersep 900 (OH^- form) in methanol. Again, it was found expedient to heat these reactions under



Scheme 6.34

microwave irradiation rather than conventional thermal conditions reducing reaction times from 6 h to less than 1 h, whilst maintaining an almost quantitative yield.

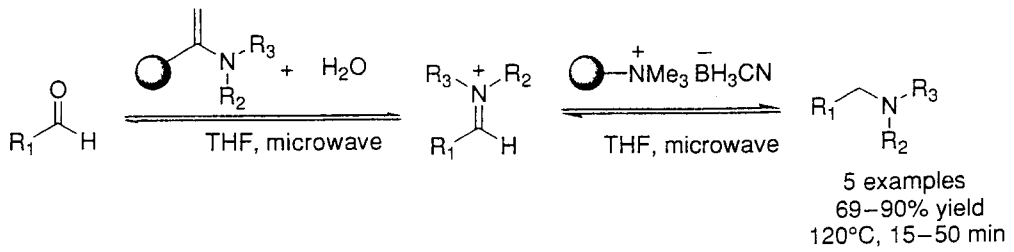
The advanced intermediate **23** also proved to be an ideal candidate for microwave-assisted synthesis. In the penultimate step of the synthesis, the secondary amine **21** was required to undergo alkylation with the phenolic halide **22**; however, this proved to be a very slow and troublesome reaction. Traditional thermal heating of the reaction with various immobilised bases produced complex mixtures, which were difficult to separate. Alternatively, a procedure using a supported carbonate reagent was found to be ideal for this conversion when used in acetonitrile under microwave irradiation conditions. Unusually, a heating sequence employing 2 × 15 min pulses maintained at 140°C with cooling to ambient temperature between cycles gave a higher yield than a single heating event. In an extended study, microwave-accelerated purification was also attempted to

enhance the rate of scavenging of excess alkyl halide **22** by employing thio-amine resin. At ambient temperature and pressure the process required 2 h, but employing a short microwave heating sequence (optimised to 10 min at 65°C) facilitated a more rapid purification, but was accompanied by a lower isolated yield (74% compared to 90%).

6.3.23. *Microwave-assisted scavenging reactions*

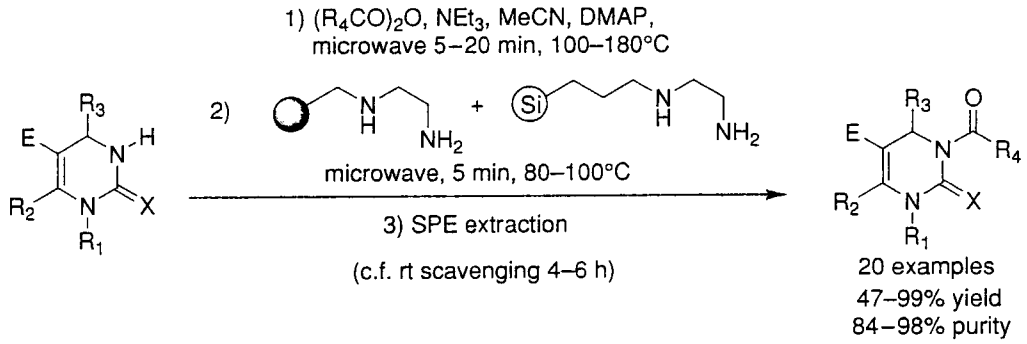
The general use of microwave heating to promote higher rates of scavenging in the purification of mixtures has received almost no coverage in the chemical literature. This is despite the extensive investigations that have been pioneered by many industrial medicinal chemistry and combinatorial groups. One of the most amenable reactions to this form of assistance is the removal of residual aldehydes, ketones and amines, by imine (enamine) formation with a reciprocally functionalised resin. Normally these reactions can be quite slow, especially when bulky or electronically retarded substrates are involved, and in these cases flash microwave heating has been identified as being highly beneficial. As previously mentioned, microwave-promoted reactions involving imine formation and the subsequent reduction by immobilised reducing agents have been used to prepare diverse libraries of functionalised amines. In many of these cases, it was found to be more efficient to use an excess of one component resulting in impure products. It is then possible to add a secondary purification step, involving the dispensing of an appropriately substituted resin (to form the imine/enamine) followed by a repeated heating cycle. The solvents of choice for these transformations have usually been THF or toluene, although a few examples have utilised alcoholic solvents for reasons of enhanced solubility and increased reactivity. Again many of these reactions are carried out at temperatures above the normal boiling points of the solvents in pressurised reaction vessels, which can assist in establishing advantageous equilibrium positions.

One especially interesting experiment that the authors have encountered involved the equilibrium transfer of an amine, which was immobilised on a resin as the enamine species (Scheme 6.35) (I.R. Baxendale, and S.V. Ley, unpublished results). This resin was added in stoichiometric excess to a 'wet' THF solution of a ketone and an immobilised cyanoborohydride resin, followed by a relatively short microwave heating sequence. This resulted in an essentially pure solution of the required amine product, which was both cleaner and was also obtained in a higher yield than any other method attempted. It is worth pointing out that this particular case represented a very specific set of examples and no additional effort was made to determine its generic applicability.



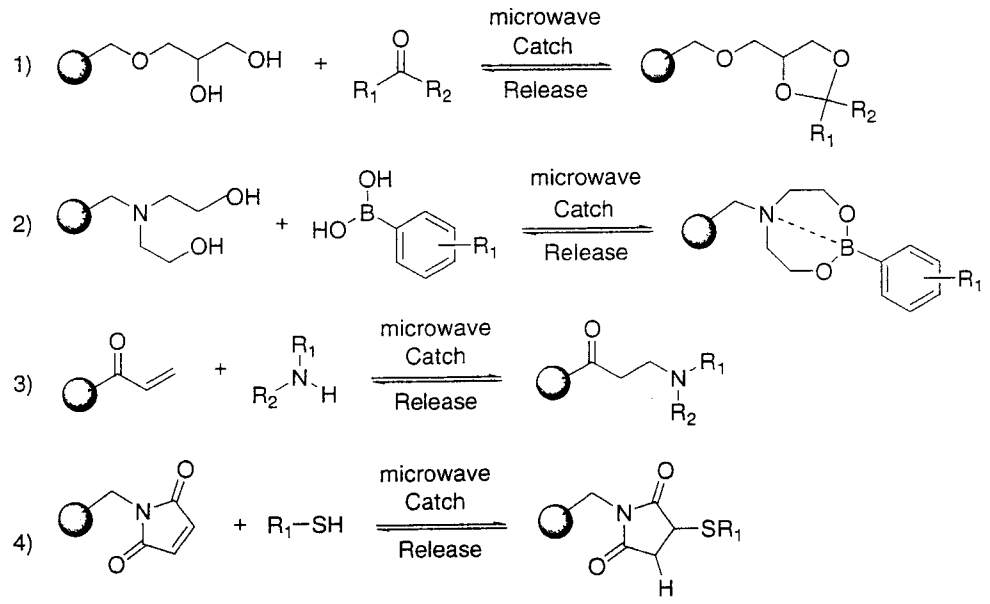
Scheme 6.35

Additional sequestering protocols have been conducted using both polymer-supported and silica-supported isocyanates, isothiocyanates, anhydrides and acid chloride species. The latter two have proved especially effective for the accelerated removal of normally difficult heterocyclic amines and anilines. Again, flash heating techniques have been applied resulting in high internal temperatures and pressures. This form of microwave heating is also conducive to the removal of electrophilic components from reaction mixtures. Anhydrides, acid halides, isocyanates and activated α-halo compounds have all been successfully scavenged from solution in shorter periods of time, when mediated by microwave dielectric heating. Kappe and co-workers[182] have recently published the synthesis of acylated dihydropyrimidines, where in part of their synthetic scheme they employed a microwave-assisted scavenging procedure to remove excess anhydride from the mixture (Scheme 6.36). This approach drastically reduced the synthesis time by shortening the scavenging periods from between 4 and 6 h at ambient temperature to less than 10 min under the directed microwave heating.



Scheme 6.36

With the multiple applications of microwave-assisted scavenging being readily applied to chemical synthesis, it is initially slightly surprising that no mention so far has been made of its use in a 'catch and release' procedure. On further consideration, the rate enhancements pertaining to the majority of the above chemistry would certainly not be as pronounced. Much of the standard catch and release methodology is based on ionic exchange interactions, which inherently display relatively high operating kinetics. However, a few examples of catch and release procedures exist, which involve the formation and cleavage of covalent bonds, where the potential arises for enhancing the reactions. This has indeed been realised with a number of processes, although in general the cases described are from industrial applications where the scavenged material was either a very valuable component or an advanced intermediate (Scheme 6.37) (I.R. Baxendale and S.V. Ley, unpublished results). The first two examples illustrate the removal of small quantities of unreacted starting materials that could be released and recycled in subsequent conversions. The third and fourth sequences represented a solution to a slightly different problem. In these two cases, an impurity in the reactions could not be separated from the product by any conventional methods attempted, and the following reactions were incompatible with the contaminating species. Here a catch and release



Scheme 6.37

sequence was performed using a stoichiometric amount of the immobilised reagent to sequester and purify the desired product. In principle, all the examples above could be used in a reverse sense to scavenge the reciprocally functionalised species. For example, an immobilised boronic acid or aldehyde could easily be applied for the separation of diols; such reactions have already been proven to work at room temperature although they require relatively long reaction times.

6.4. Conclusion

Microwave flash heating can provide a set of reaction parameters that permit the stimulation of a reaction, without the requirement for a prolonged or ecliptic heating profile. In this way, many reactions that would normally suffer significant thermal degradation can be performed as a result of the shortened reaction times. Gross and local pressure changes created during the reaction heating can also be important in enhancing the rate of reaction. At present, this is an area that is recognised but is undervalued and under utilised. Although extremely advantageous, it should be noted that any approach reliant on a purely thermal enhancement, independent of the heating mechanism, depends significantly on the stability of the product and reagents used.

Many of the examples mentioned have been directly concerned with, or have a consequential importance, to the area of parallel high throughput chemical processing. Any methodology that offers the ability to accelerate the synthesis of large chemical libraries or to access new chemical entities in a clean fashion needs careful consideration. It is certainly true that we have only just begun to comprehend and contemplate the possibilities that the combination of these two powerful technologies could offer. It is therefore hoped that this short chapter will in some way stimulate you, the reader, to have a new outlook on these synthetic methods.

6.5. References

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