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Microwave Assisted Organic Reactions

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1. Introduction

The rapid heating of foodstuffs in microwave ovens is routinely used by a significant proportion of mankind. However people have recognised other potential applications for this method of heating and scientists engaged in a number of disciplines have applied the rapid heating associated with microwave technology to a number of useful processes. These include the preparation of samples for analysis[1]; applications to waste treatment[2]; polymer technology[3]; drug release/targeting[4]; ceramics[5] and alkane decomposition[6]. The technique has also found use in a range of decomposition processes including hydrolysis of proteins and peptides[7]. Application to inorganic and solid state synthesis has also been shown to have significant advantages[8]. The purpose of this review is to highlight the applications of microwave radiation to organic reactions[9,10]; organic synthesis is an area which can benefit significantly from this technology[11].

2. General Principles

The microwave region of the electromagnetic spectrum lies between 1cm and 1m and in order to avoid interfering with radar and telecommunication activities which operate within this region, most domestic and commercial microwave instruments operate at 2.45GHz. The heating effect utilised in microwave assisted organic transformations is due in the main, to dielectric polarisation, although conduction losses can also be important particularly at higher temperatures. Whilst the polarisability of a molecule (determined by the Debye equation) is the sum of a number of contributions, only dipolar and interfacial polarisation are important to heating effects associated with microwave irradiation. When a molecule is irradiated with microwaves it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continually attempts to realign itself with the changing field and energy is absorbed. The ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature is calculated using the following equation ($\varepsilon''/\varepsilon' = \text{Tan } \delta$). Where δ is the dissipation factor, ε'' is the dielectric loss-which measures the efficiency with which heat is generated from electromagnetic radiation and ε'-the dielectric constant i.e. the ability of a molecule to be polarised by an electric field. The interfacial polarisation, the Maxwell-Wagner effect, may also contribute to the heating effect when the conducting particles are in contact with a non-conducting medium, e.g. in heterogeneous reactions. It is particularly convenient that qualitatively, the larger the dielectric constant, the greater the coupling with microwaves. Thus solvents such as water, methanol, DMF, ethyl acetate, acetone, chloroform, acetic acid and dichloromethane are all heated when irradiated with microwaves. Solvents such as hexane, toluene, diethyl ether, CCl_4, do not couple and therefore do not heat with microwave irradiation although it is of course possible to use mixtures comprising microwave active/microwave inactive solvents.

3. Experimental Considerations

In a microwave oven radiation is generated by a magnetron, the microwaves are guided into the cavity by a waveguide and reflected by the walls of the cavity. If the microwaves are not absorbed they may be reflected back down the waveguide and damage the magnetron; thus it is essential to have a microwave active "dummy load" which will absorb excess microwaves and avoid such damage. There are a variety of methods for carrying out microwave assisted organic reactions using domestic or commercial ovens.

3.1 Domestic Microwave Ovens

The relatively low cost of modern domestic microwave ovens makes them reasonably readily available to academic and industrial chemists; however somewhat surprisingly only a relatively small number of organic synthesis research groups have reported their use[12]. One disadvantage is that the variable power levels are produced by simply switching the magnetron on and off; this may be problematic if reaction mixtures cool down rapidly. Notwithstanding this limitation there are a number of useful reactions that one can carry out in a domestic microwave oven.

3.1.1 Non-Solid-State Reactions

It is possible to carry out reactions under traditional conditions in which the reagents are dissolved in an organic solvent. The experimental procedure can be extremely simple; reactions can be carried out in open erlenmeyer flasks and subjected to short periods of irradiation[13]. It must be noted that this procedure can only be carried out if neither the solvent or the reactants or products are flammable, otherwise there is a serious risk of fire or explosion due to sparking. Included in this survey are a number of reactions which are carried out employing this method, usually using DMF as solvent. In addition to the significant practical simplicity of this type of procedure, it is sometimes found that volatile reaction by-products evaporate rapidly thus avoiding methods for their specific removal. Reactions may also be carried out in sealed systems (see under vessels) although there are also limitations to this approach.[14] Of course if one wishes to carry out a thermally driven reaction in a microwave oven then one of the components must be microwave active. If neither the reagents or solvents couple then it may be possible to use a microwave active additive or supported metal catalyst to generate heat.[15] It should be noted that some of these inorganic additives can easily reach temperatures in excess of 1000°C[16] very rapidly and decomposition of materials may be problematic, therefore the same precautions regarding superheating and associated fire hazards or explosions should be taken.

3.1.2 Solid-State-Reactions

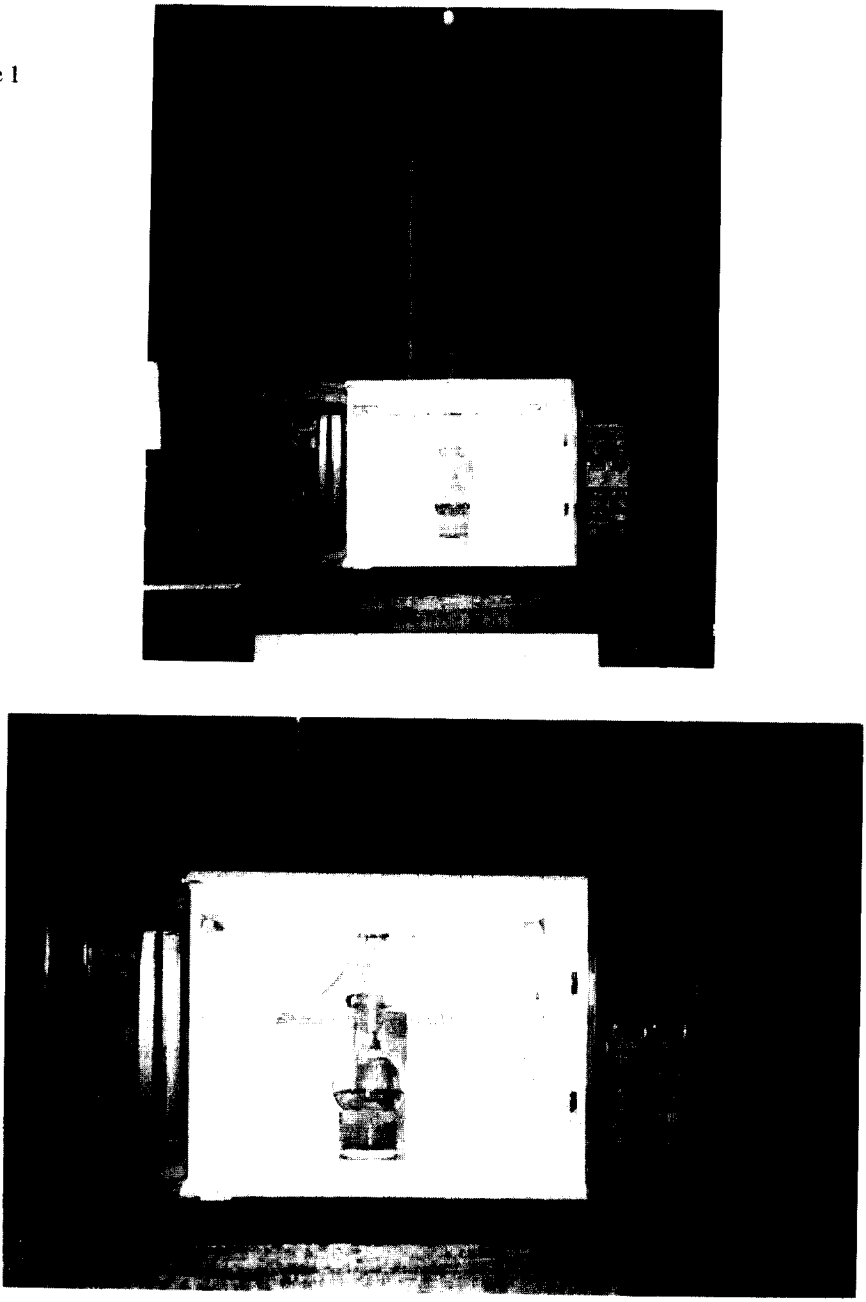
A number of interesting reports have illustrated the utility of this type of reaction. Whilst a number of transformations carried out in the solid state have been known for some considerable time, the use of microwave radiation does appear to extend the scope of such appealing reactions. There are generally two types of microwave assisted dry reactions; one in which the reagents are "supported" on a microwave inactive (or poorly active) material such as alumina/silica.[17] In this type of reaction at least one of the reagents must be polar if the reaction is to benefit from microwave irradiation. The second type of dry reaction will utilise a microwave active solid support, thus the reactants do not have to be microwave active.

Solid-state reactions are of course very convenient from a practical viewpoint, in general the reagents and solid support are efficiently mixed in an appropriate solvent which is then evaporated. The adsorbed reagents are then placed in a vessel and subjected to microwave irradiation after which the organic products are simply extracted from the support by washing and filtration. The absence of solvent coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for synthesis.

3.1.3 Modification of Domestic Microwave Ovens

There are a number of published methods for the safe modification of domestic microwave ovens[18]; scheme 1 shows a modified oven used in the author's laboratory. The improved safety of this type of system is particularly attractive; the advantage of modifying an oven in this way is that the reaction vessel is neither sealed or directly open to the microwave oven; thus reactions can be carried out using a flask attached to a reflux condenser.

Scheme 1



There are two advantages of using this type of system (i) A wide variety of solvents can be used because the fire hazard is significantly reduced compared to an open vessel system (ii) Reactions can be carried out under inert conditions. Recent reports have also detailed the use of continuous microwave reactors for organic transformations.[19]

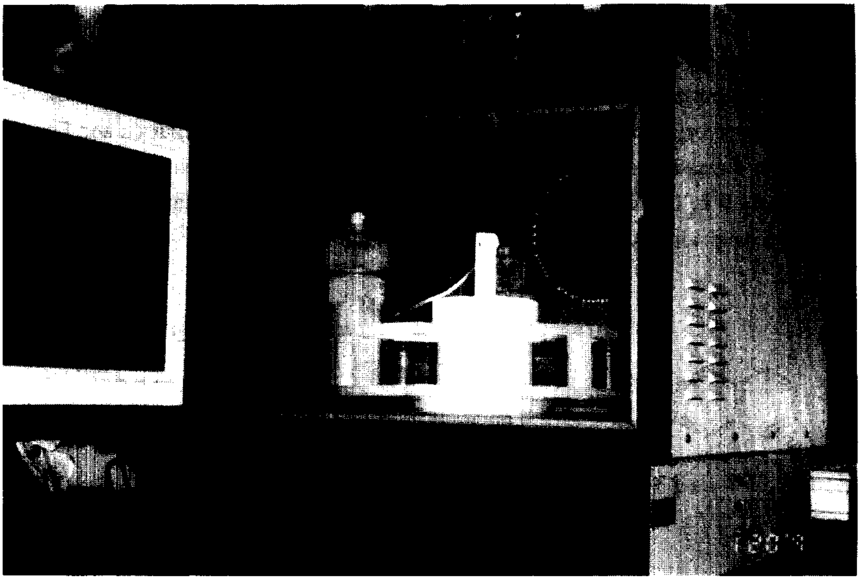
3.2 Vessels

Microwave assisted reactions can, under the appropriate conditions, be carried out using conventional vessels pyrex, PTFE etc. However, if reactions are to be carried out under pressure in sealed systems the major concern is the ability of the vessel to withstand the changes in pressure and temperature associated with the particular transformation. The rapid increases in temperature and pressure associated with microwave promoted superheating of organic materials makes it very difficult to ensure the safety of this type of procedure. It is essential that great precautions are taken when carrying out reactions in sealed vessels. The technology of vessel design is improving and a range of vessels are now available for carrying out reactions under pressure[20]; many incorporate pressure releasing systems as an additional safety measure. An alternative simple procedure suitable for small-scale experiments is to seal the reagents in pyrex vials, surround them in vermiculite and irradiate with microwaves, however great care must be taken when using this type of protocol.

3.3 Commercial Systems

The commercial system is a more expensive way of carrying out microwave assisted organic reactions. A number of systems are currently available although these have mostly been developed for analytical applications; an example of one system used in the author's laboratory is manufactured by CEM Microwave Technology Ltd., and is shown in scheme 2.

Scheme 2



This type of system operates with a rotating carousel, so that a number of reaction vessels can be irradiated and agitated at the same time. The vessels are made of poly(etherimide) with teflon inserts and it is possible to monitor both the internal temperature and pressure of the reaction. Additional advantages of this type of system are the incorporation of a "microwave active" dummy load to protect the magnetron and the more reliable, accurately controlled and continuous source of microwave radiation produced. The monitoring of temperature is a significant issue if one is attempting to compare microwave and conventionally heated reactions. A number of approaches have been used including the use of a fibre optic probe[11]; a gas thermometer[21]; thermochromic paints[22] and infrared pyrometry[11].

3.4 Solvents

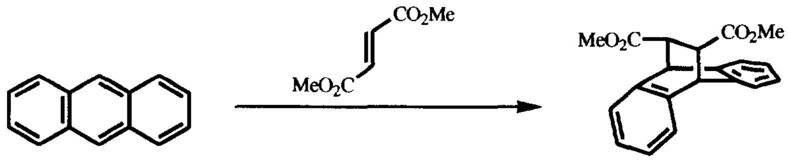
As previously mentioned, if the solvents are to be used as the source of heat then they must couple effectively with microwave radiation. Whilst various solvents can be used a number of factors need to be considered. The type of vessel used may be incompatible with certain solvents and with open vessel systems flammability and volatility are both important issues. Solvents such as DMF, MeCN and CH_2Cl_2 are all useful for particular kinds of reaction but obviously there are some limitations to each. The use of water is appealing and has been noted by several groups, however a number of interesting opportunities are still to be developed and this may be a fruitful area of future activity. It has been shown that with microwave irradiation solvents can be heated above their boiling points and it may be argued that it is this form of superheating which leads to observed rate enhancements for many reactions[23].

4.1 Microwave Assisted Reactions in Organic Solvents

In this section we will examine examples of organic transformations which have been carried out by using microwave energy to heat "traditional" reaction mixtures; thus in most of these reactions a solvent is utilised. In the majority of the cases included in this section the reagents are dissolved in a solvent which couples effectively with microwaves and generates the heat energy required to promote the transformation. The opportunities which such technology offers to synthetic organic chemists were first highlighted in two important contributions from Gedye, Smith and Westaway[9] and Giguere, Majetich and co-workers.[10]

4.1.1. Pericyclic Reactions

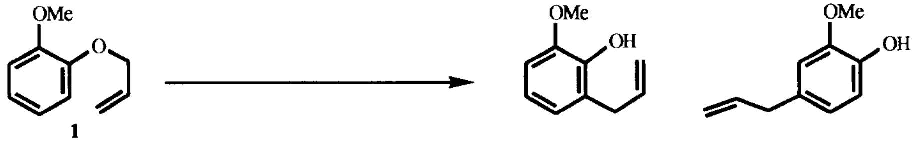
In 1986 in their important early contributions Giguere, Majetich[10] and co-workers highlighted the potential of microwave assisted organic reactions by illustrating that the Diels-Alder, Claisen and Ene reactions could be carried out with dramatic reductions in reaction times. Thus Diels-Alder reaction of anthracene with dimethyl fumarate proceeds in 10 minutes in *p*-xylene (87%) whereas under conventional thermolysis conditions the reaction proceeds in 4 hours (67%) as illustrated in scheme 3.



Microwave	Control
10 min,	4 hours
p-Xylene, 87%	p-Xylene, 67%
325°C<361°C	138°C

Scheme 3

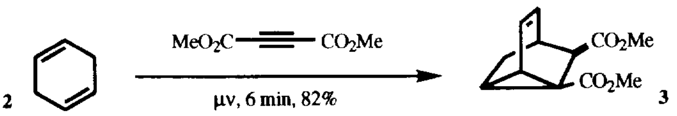
The crucial interplay of reaction time, temperature and solvent is illustrated in the Claisen rearrangement of allyl ether **1** (scheme 4). It was found that, when carried out in the absence of solvent, conventional thermolysis provided the rearranged product with improved yields with reduced reaction time (45 versus 12 minutes). Under microwave assisted conditions an 87% yield of products was isolated when the reaction was carried out in N-methylformamide as depicted in scheme 4.



Microwave	Control
12 min, neat, 370<400°C,71%	12 min, neat, 320°C,92%
5 min, DMF, 300<315°C,72%	45 min, neat, 265°C,71%
90 sec, NMF, 276°C, 87%	

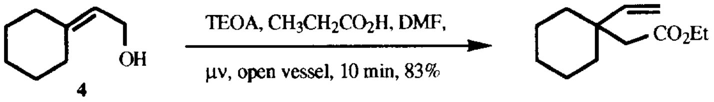
Scheme 4

The same group also highlighted the potential of microwaves to promote synthetically appealing sequences. Thus the transformation of **2** to **3** *via* the Alder-Bong reaction was optimised at 82%. Although the product can also be similarly isolated under conventional conditions, the short reaction time associated with the microwave assisted procedure is very attractive. It should be noted that these reactions were carried out in sealed glass ampoules[24].



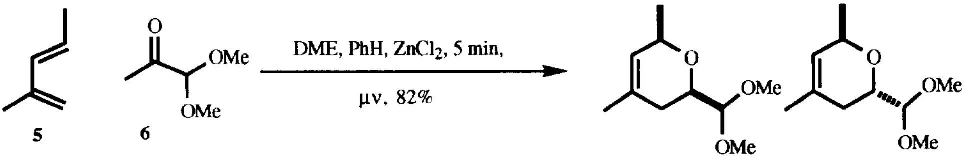
Scheme 5

Srikrishna and Nagaraju have also examined microwave assisted pericyclic processes[25], they have illustrated that Claisen rearrangement of the ketene-acetal derived from alcohol **4** proceeds in 83% yield in ten minutes as oppose to 48h in a sealed tube. It is worth noting that the presence of boiling chips leads to evaporation of solvent and reduction in yield.



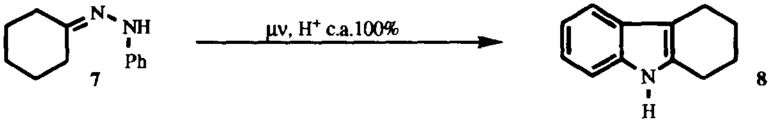
Scheme 6

Further studies by Stambouli, Chastrette and Soufiaoui[26] have demonstrated the benefits of microwave irradiation for the isolation of products from hetero-Diels-Alder reaction. Thus cycloaddition of diene **5** with dienophile **6** under microwave irradiation leads to products in good yields, whereas under conventional heating no products are isolated after 4 hours at 140°C.



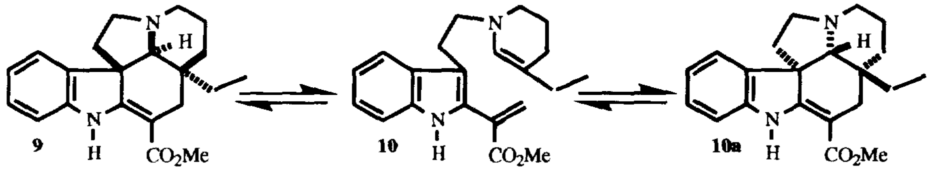
Scheme 7

The Abramovitch group have demonstrated the application of microwave technology to [3,3]-sigmatropic rearrangements involved in Fischer cyclisations[27]. They have found that irradiation of **7** in formic acid in a Parr bomb produced product **8** in excellent yields.



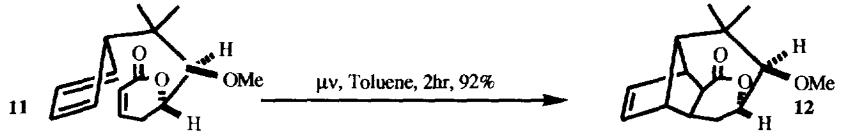
Scheme 8

An efficient racemisation in DMF has been reported by Takano and co-workers[28]; thus cycloreversion of **9** to secodine intermediate **10** then furnishes **10a** *via* [4+2] cycloaddition. The reaction is reported to proceed less efficiently under conventional heating and the optimum conditions require microwave irradiation in DMF for 20 minutes.



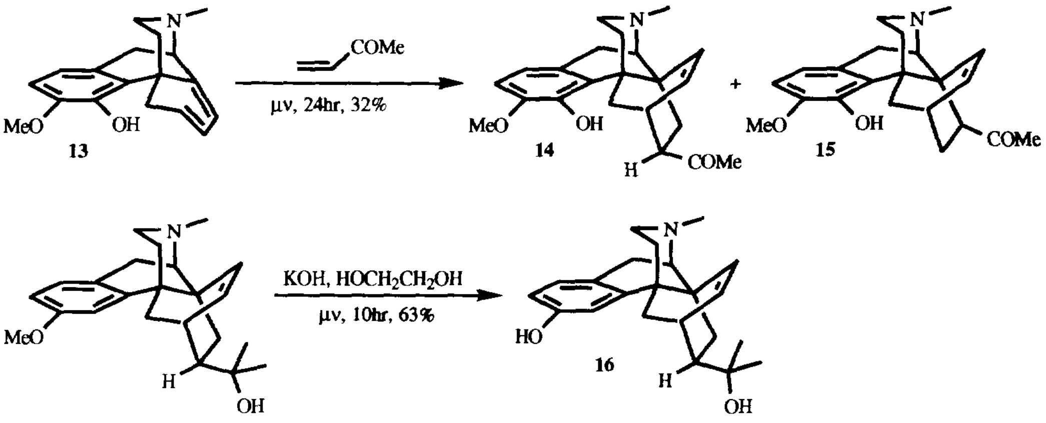
Scheme 9

Fallis and Lei have utilised a microwave assisted intramolecular Diels Alder reaction (**11** to **12**) as a key step in the synthesis of (+) Longifolene as shown below[29].



Scheme 10

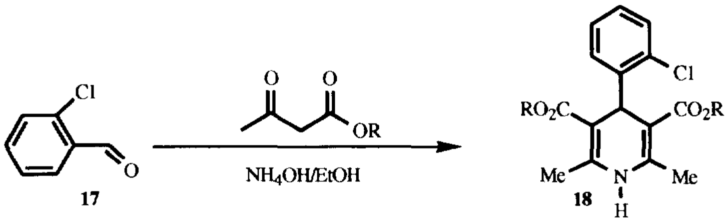
Linders, Kokje and co-workers have utilised microwave assisted reactions in the preparation of morphinan analogues[30]. They claim that the isolation of cycloadducts **14** and **15** from the reaction of thebaine derivative **13** with methyl vinyl ketone is greatly simplified and requires reduced reaction times. At a later stage they utilise a microwave assisted demethylation procedure to furnish the target molecule **16** in reasonable yield.



Scheme 11

4.1.2. *Cyclisation Reactions*

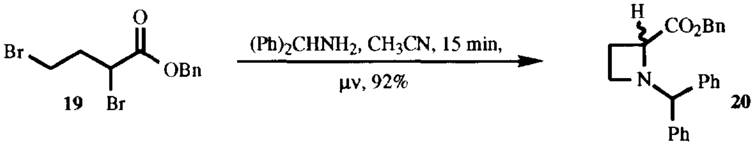
Microwave irradiation has been used to improve other types of cyclisation reaction as illustrated by Alvarez-Builla and co-workers in their microwave assisted Hantsch-1,4-dihydropyridine synthesis[31]. Reduced reaction times and improved yields are generally associated with this procedure as exemplified in the preparation of **18** from **17** in 55% yield.



μv (%, time sec)	Control (%, time hr)
55, 4	44, 24.

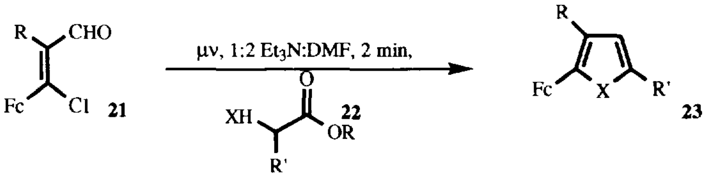
Scheme 12

In the preparation of novel four membered oxazoborolidines Rao and co-workers utilise a highly efficient microwave assisted cyclisation reaction[32]. Thus transformation of **19** to **20** using the literature procedure required 24 hours at reflux (82%). Microwave irradiation dramatically reduced the reaction time to 15 minutes with an improvement in the isolated yield (92%).



Scheme 13

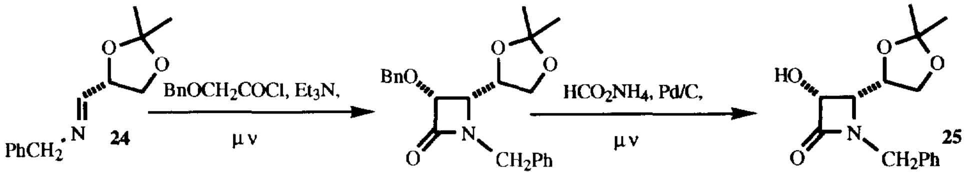
Puciova, Ertl and Toma have utilised microwaves in the preparation of ferrocenyl (Fc) substituted heteroaromatic systems[33]. Thus treatment of ferrocenyl substituted acrylaldehyde **21** with ester **22** gives heterocycles **23** in moderate to good yield as illustrated in scheme 14.



X = S, R' = H, 87%
X = O, R' = H, 35%

Scheme 14

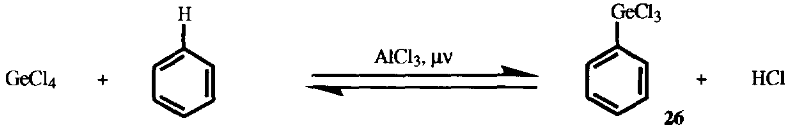
The preparation of enantiomerically pure β-lactams using microwave technology has been described.[34] Thus the authors claim the preparation of 25g of **25** from **24** with a days effort using two microwave assisted reactions as shown below.



Scheme 15

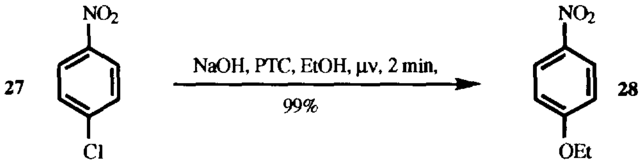
4.1.3. *Aromatic Substitution Reactions*

The efficiency of aluminium chloride catalysed Friedel-Crafts germylation of benzene and toluene is enhanced using microwave irradiation. Thus germylation of benzene under standard reflux conditions provides **26** in 20% yield after 24 hours. A slight improvement in the yield of this reaction can be achieved using microwave irradiation; two hours microwave irradiation provides the product **26** in 25% yield[35].



Scheme 16

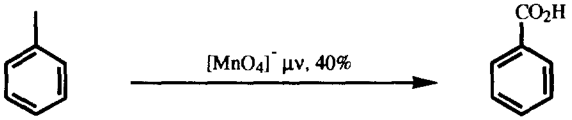
Nucleophilic aromatic substitution has been enhanced using microwave irradiation, judicious choice of phase transfer catalyst is essential for optimal yields. The authors quote rate enhancements of 144 -240 fold in transformations exemplified in the highly efficient preparation of **28** from **27**[36].



Scheme 17

4.1.4. *Oxidation*

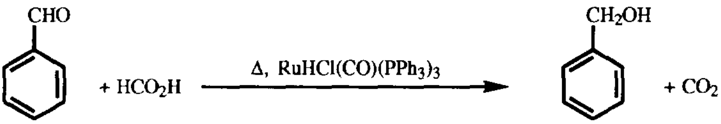
The oxidation of toluene with permanganate has also been reported to proceed rapidly under microwave conditions[9] (scheme 18). The reaction proceeds in 40% yield after five minutes of microwave irradiation; unfortunately attempts to optimize the process were curtailed when it was found that very high pressures led to an explosion, this highlights the care that workers need to take when investigating the application of microwave thermolysis to organic reactions.



Scheme 18

4.1.5. *Catalytic Transfer Hydrogenation*

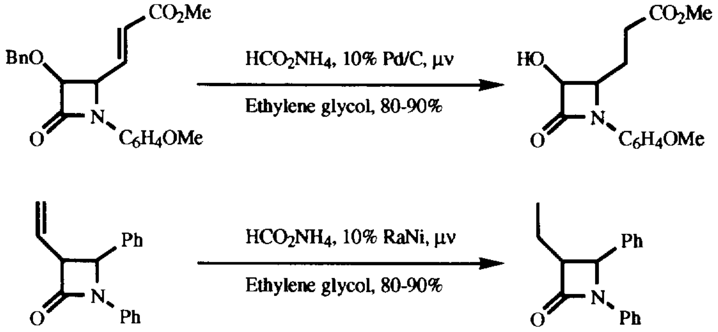
A recent report has examined the effect of microwave irradiation on the hydrogenation of benzaldehyde using $RuHCl(CO)(PPh_3)_3$[37].



Scheme 19

The authors compared the transformation under traditional reflux conditions with either intermittent or persistent microwave irradiation and found that with constant microwave irradiation the reaction was completed in 7 minutes as compared with 3 hours under standard reflux. The authors also note that differences associated with catalyst batch were more pronounced in the microwave assisted process.

Bose and co-workers have reported hydrogenation of substituted β-lactams using Pd/C or Raney nickel as shown in scheme 20[38].

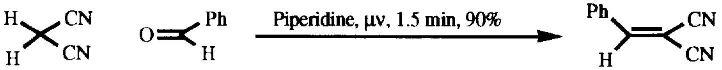


Scheme 20

The authors note similar reaction times to those carried out with a preheated oil bath at 130°C on a small scale, however on the larger scale microwave assisted reactions appear to proceed more rapidly.

4.1.6. *Alkene Synthesis*

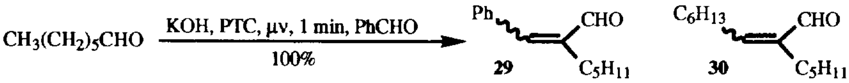
It has been demonstrated that alkenes can be prepared in an experimentally simple procedure by Knoevenagal condensation of active methylenes with carbonyl groups as illustrated below (scheme 21).



Scheme 21

The reactions are carried out in an open vessel from which the water is vapourised, thus avoiding the requirement of a Dean-Stark apparatus. The products are isolated and purified by washing with solvent or by short path distillation[39].

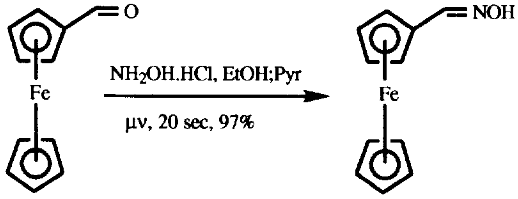
The preparation of Jusminaldehyde **29** was achieved in 82% if the reagents are thermolysed using microwave radiation[40]. Thus treatment of benzaldehyde with *n*-heptanal under PTC conditions and irradiation for one minute gives a mixture of products comprising the desired product **29** (82%) and self condensation product **30** (18%).



Scheme 22

4.1.7. *Oximes*

The preparation of ferrocenyl oximes has been described by Puciova and Toma[41] as shown below, the authors claim that in contrast to conventionally heated reactions, the microwave assisted reactions gave only the thermodynamically stable isomer (scheme 23).

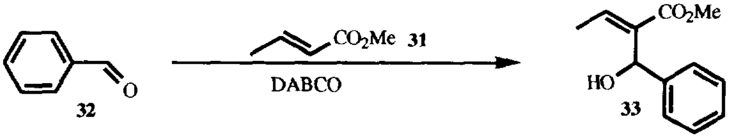


Scheme 23

For some of the examples described the authors carry out the reactions in an erlenmeyer flask fitted with a small condenser, using hexane as a cooling medium.

4.1.8. Alkene Functionalisation

Recent work by Bhat and co-workers[42] has demonstrated the utility of microwave irradiation to the Baylis-Hilman reaction. This synthetically useful reaction which can be almost prohibitively slow can be enhanced by altering a number of parameters including pressure and temperature or by using ultrasound. The authors report that by carrying out reactions under microwave irradiation in a sealed tube, improved yields of product can be isolated with substantial reductions in reaction times. Thus treatment of benzaldehyde **32** with methyl crotonate in the presence of DABCO leads to the product **33** in 10 minutes as opposed to the two days required at room temperature.

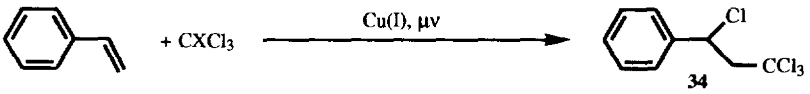


μv (%, time, min)	Conventional (%, time, days)
34, 10	25, 2

Scheme 24

In general the reactions were carried out by heating the neat reagents, although methanol was reported as an effective solvent for one of the examples given.

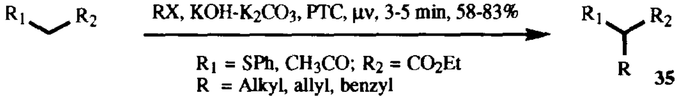
Adamek and Hajek, have illustrated the copper catalysed addition of chlorinated hydrocarbons to styrene as illustrated below in the isolation of **34**[43].



Scheme 25

4.1.9. Alkylation Reactions

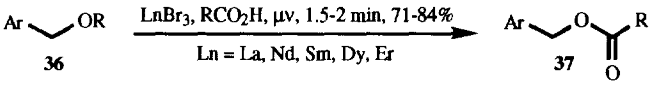
Yaozhong and co-workers have reported phase transfer promoted microwave assisted C-alkylation of active methylenes as illustrated below[44].



Scheme 26

The authors report generally good selectivity for monoalkylated products **35**, and that the reactions can be carried out in toluene to ensure efficient mixing of the reagents.

Carboxylic esters have been readily prepared by a tribromolanthanoid mediated deetherification reaction highlighted below[45] (scheme 27). Thus microwave irradiation of benzyl ether **36** with a carboxylic acid in the presence of $LnBr_3$ led to the isolation of ester **37** in 61-84% yield. The reactions are dependant upon the presence of the $LnBr_3$; in its absence yields are significantly reduced.

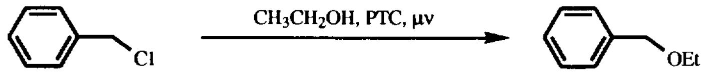


Scheme 27

When a similar transformation was attempted using a dialkyl ether as opposed to an arylalkyl ether yields were much lower and improvements are essential for the development of a synthetically useful process.

An alternative microwave assisted method for promoting esterification utilises phase transfer catalysis; irradiation of potassium acetate with alkyl halides for 1-2 minutes (Aliquat 336, 5-10%) gives the product in good to excellent yields 60-98%[46].

In a recent report[47] the effect of microwave irradiation on phase transfer assisted ether synthesis was examined. In the examples investigated the effect was beneficial, leading to dramatically shorter reaction times with similar or better yields of isolated products. Thus the reaction of benzyl chloride with ethanol was significantly accelerated using microwaves (scheme 28).

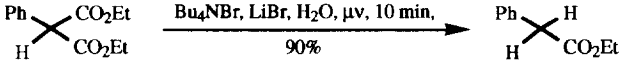


µv (%, time min)	Control (%, time min)
85, 5	66, 1440

Scheme 28

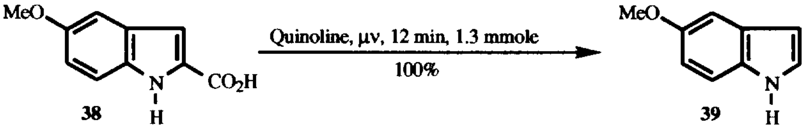
4.1.10. Decarboxylations

Loupy and co-workers have shown that phase transfer catalysed dealkoxycarboxylations can be promoted using microwave irradiation[48] (scheme 29)



Scheme 29

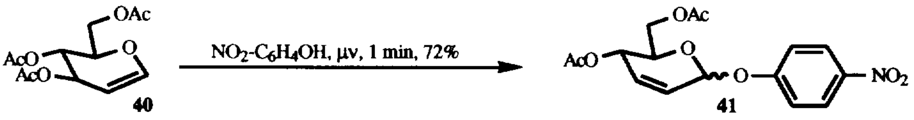
Jones and Chapman have developed a very useful method for the decarboxylation of indole-2-carboxylic acids. Thus microwave thermolysis of a suspension of substituted indole **38** with quinoline led to the isolation of product **39** in quantitative yield[49]. The efficiency of this procedure extends the synthetic utility of the range of useful 2-substituted indole syntheses currently available.



Scheme 30

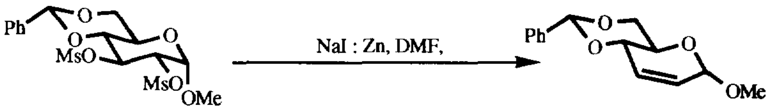
4.1.11. Carbohydrates

Microwave irradiation of tri-O-acetyl-D-glucal with a range of alcohols led to the isolation of Ferrier rearrangement products in good yield as exemplified in the transformation of **40** to **41** below. Although conventional thermolyses also leads to the desired product in similar yields (several hours) the new procedure does offer a useful alternative[50].



Scheme 31

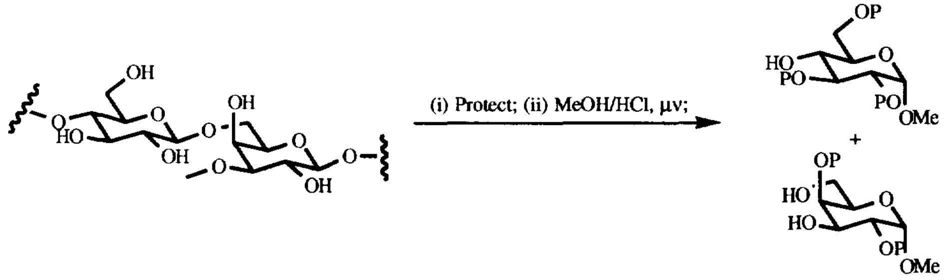
The preparation of unsaturated pyranosides by the microwave assisted Tipson-Cohen reaction has also been studied as depicted below in scheme 32. Thus irradiation of a mixture of mesylates or tosylates with sodium iodide and zinc dust in DMF with microwaves led in general, to improved yields and reduced reaction times when compared to more conventional heating conditions[51].



μv (%, time min)	Conventional (%, time min)
89, 8	42, 120

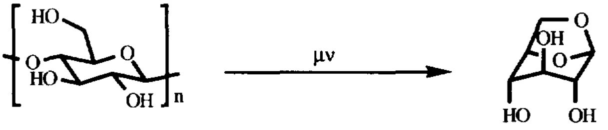
Scheme 32

Nakanishi and co-workers have described an interesting methanolysis procedure; they report that microwave irradiation of suitably protected oligosaccharides leads to the isolation of products with anomeric inversion[52] (scheme 33).



Scheme 33

Straathof and co-workers have described the preparation of 1,6-anhydroglucose from (1-4)-D-glucans; thus microwave irradiation of starch leads to the isolation of **42**[53] (scheme 34).



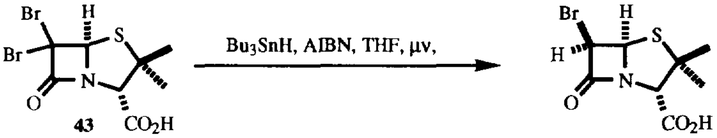
42

Scheme 34

Although the yields are low (c.a. 0.5 to 2%) the simplicity of the procedure makes it an attractive method for the production of small quantities of **42** (1-300mg).

4.1.12. Radical Reactions

Bose and co-workers have described the application of microwave radiation to the TBTH mediated reduction of β-lactams as shown in the reduction of **43**[13] (scheme 35).



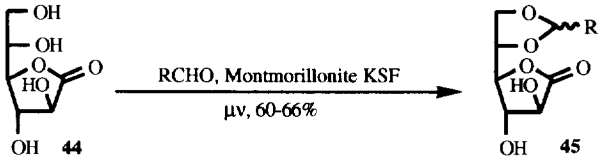
Scheme 35

4.2 Microwave Assisted Organic Reactions in the Absence of Solvent

In this section we will be highlighting a number of useful reactions which in general, proceed without organic solvent[54] often using some type of inorganic material as either a catalyst/promoter or as a support. In a few cases included in this section a reaction solvent is used; however a certain amount of overlap is inevitable with the classification system used in this survey.

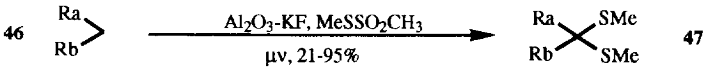
4.2.1. Protecting Groups

Functional group protection and deprotection strategies are central to target synthesis and microwave irradiation has been shown to be of particular utility in this area. It has been found that acetals of l-galactono-1,4-lactone can be efficiently prepared using this technology. Adsorption of lactone **44** and an appropriate aldehyde onto montmorillonite KSF and irradiation with microwaves for 10 minutes led to the isolation of product **45** in good yield[55]. The yields were dramatically improved using this procedure as compared with the classical method (DMF, $40^{\circ}C$, H_2SO_4, $CuSO_4$, 22-38%).



Scheme 36

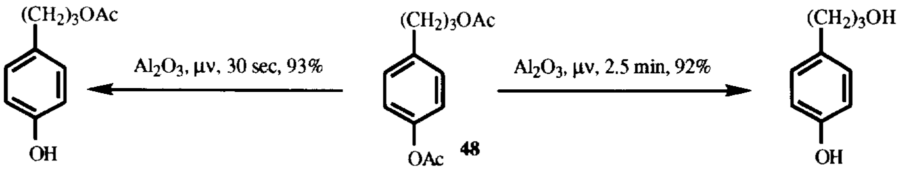
Villemin and co-workers have also developed a useful approach to dithioacetals. Adsorption of active methylenes of the type **46** with Al_2O_3-KF and methanesulphonothioate and irradiation with microwaves leads to the product **47** in moderate to excellent yields as shown below[56].



Ra and Rb = CO_2R, CN, Ph, $PO(OEt)_2$

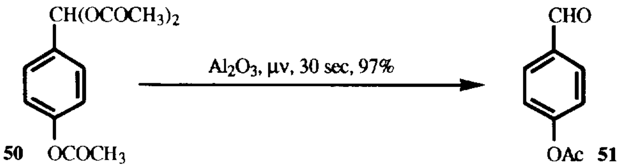
Scheme 37

Varma and co-workers have carried out extensive investigations leading to the development of a range of microwave assisted deprotection procedures. The group have found for example that selective deacetylation reactions of acetylated phenols **48** give high yields of products[57]; the analogous reactions when carried out under conventional thermolysis proceed in similar yields but require longer reaction times (c.a. 40 hours).



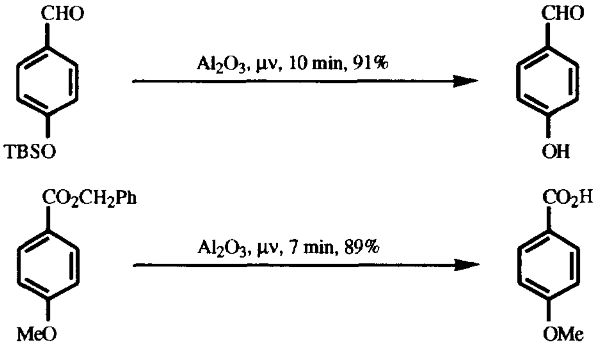
Scheme 38

A similar procedure can be used to deprotect benzaldehyde diacetates **50** leading to arylaldehydes **51** as shown below[58] (scheme 39).



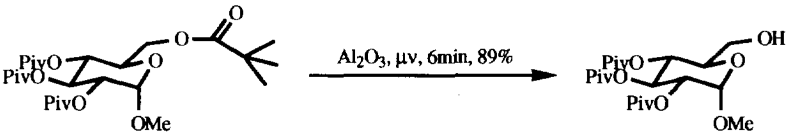
Scheme 39

It can also be applied to benzyl esters[59] and silyl ethers[60] as illustrated in scheme 40.



Scheme 40

Similar methodology has been used in the deprotection of pivaloyl and methyl esters as exemplified below in scheme 41[61] .

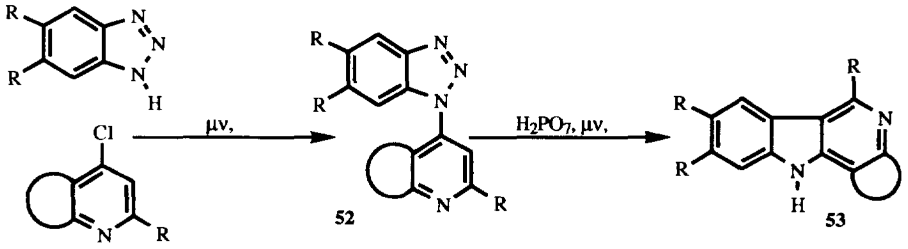


Scheme 41

It is worth noting that in order to optimise yields of most of these deprotection reactions, 10-15g of alumina per mmole substrate are required.

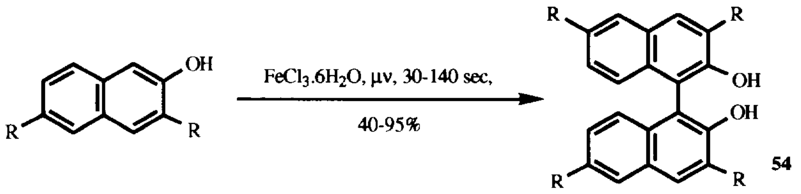
4.2.2. Aromatic Substitution

In a synthesis of β-carbolines *via* a Graebe-Ullmann reaction, Alvarez-Builla and co-workers have found that irradiation of benzotriazole and chloropyridines in the absence of solvent followed by irradiation in the presence of pyrophosphoric acid leads to moderate to excellent yields of products **53** (13-16 minutes)[62]. It is noteworthy that the authors attempted to support the reactants on silica gel or montmorillonite but unfortunately irradiation led to only moderate yields of the intermediate pyridyl benzotriazole **52** being isolated. The analogous conventionally thermolysed reactions led to the desired product in similar yields but required significantly longer reaction times (1.5-2 hours)



Scheme 42

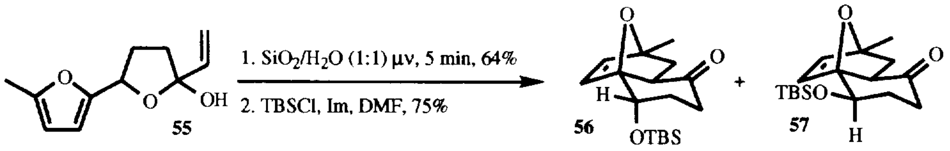
Villemin and co-workers have also developed microwave assisted biaryl synthesis[63]. Thus binaphthols **54** can be prepared in moderate to good yields by irradiation of the dry solid reagents, $FeCl_3.6H_2O$ and the appropriate naphthol in a resonance cavity.



Scheme 43

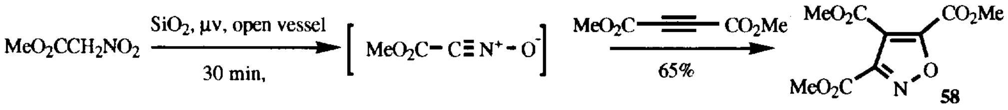
4.2.3. Pericyclic Reactions

As already illustrated a range of pericyclic reactions have been shown to benefit from microwave irradiation. Roskamp and Wang have nicely illustrated its application to intramolecular Diels-Alder reactions. It is reported that conventional thermolysis of furan **55** led to poor yields of cycloaddition due to substantial decomposition. However by adsorbing the furan onto silica gel, saturating with water and irradiating with microwaves, cycloadducts **56** and **57** were isolated in 64% yield[64]. The authors suggest that the water which is crucial for the success of this transformation, acts as a source of heat, accelerates the cycloaddition by the hydrophobic effect and promotes the hemiacetal-ketone equilibrium.



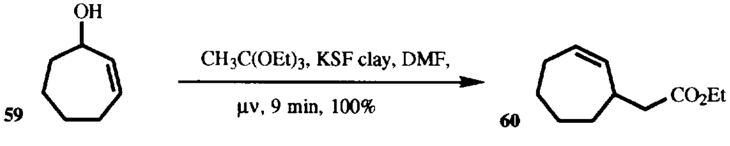
Scheme 44

Hamelin and co-workers have investigated the generation and cycloaddition of nitrile oxides. They showed that nitrile oxides could be generated by dehydration of methyl nitroacetate or dehydrohalogenation of oximes under microwave irradiation. Thus a mixture of methyl nitroacetate and DMAD in the presence of acid (SiO_2, or molecular sieves) in an open vessel gives rise to cycloadduct **58** in moderate to good yield[65] (scheme 45).



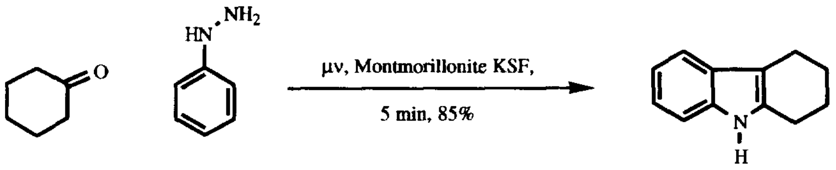
Scheme 45

Jones and Huber have demonstrated that KSF clay can be used to catalyse and accelerate ortho-ester Claisen rearrangements. An illustration is shown below in scheme 46 in which microwave irradiation of **59** with triethyl orthoacetate and KSF clay in DMF led to the isolation of rearranged product **60** in good yield. Under more conventional conditions in which propionic acid was used as catalyst (as oppose to KSF clay) the reaction required 12.5 hours heating to give a 68% isolated yield of **60**[66].



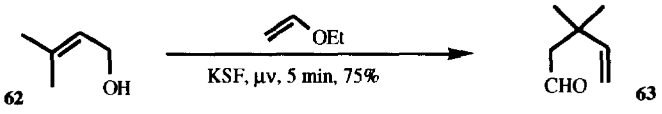
Scheme 46

Montmorillonite KSF clay has also been shown to catalyse microwave assisted Fischer indole synthesis. Villemin and co-workers have illustrated the utility of this procedure exemplified in the synthesis of **61** from cyclohexanone and phenyl hydrazine below[67] in scheme 47. Interestingly Abramowitch and co-workers report that when they used "dry conditions" for a closely related cyclisation (**7** to **8**, scheme 8) they were only able to isolate traces of product[27].



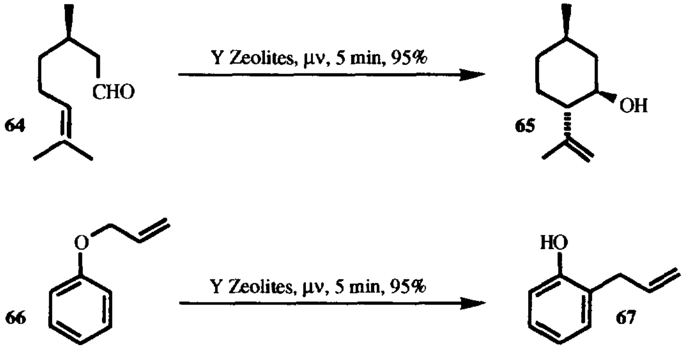
Scheme 47

Villemin and co-workers have also shown that montmorillonite clays aid other organic transformations including [2,3] sigmatropic rearrangements. Thus adsorption of **62** onto KSF clay followed by microwave irradiation (5 minutes) led to the isolation of product **63** in 75% yield[17]. When the reaction was carried out by heating under conventional conditions at 135°C for 5 minutes none of product **63** was isolated.



Scheme 48

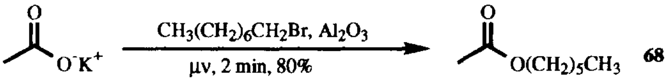
Ipaktschi and co-workers have shown that various sigmatropic rearrangements can be carried out by adsorption of the substrate on Y zeolites. Microwave irradiation of **64** gives **65** and **66** gives **67** *via* Ene and Claisen rearrangement respectively[68].



Scheme 49

4.2.4. Alkylations

Alkylation of carboxylic acids has been investigated by Loupy and co-workers who have found that high yields of alkylated product can be isolated when potassium acetate adsorbed on alumina is irradiated in the presence of an alkyl halide. Thus potassium acetate and octyl bromide give product **68** in good yield using microwave irradiation[69].

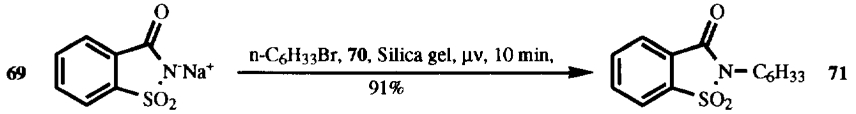


Scheme 50

The authors note that when only small quantities of materials are used an external bath of alumina aids reproducibility. However on the larger scale (up to 0.1 mole) irradiation in open vessels leads to high yields without the use of an external alumina bath.

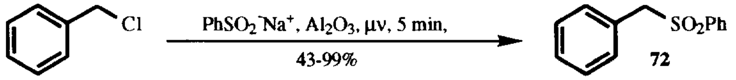
An alternative procedure has been developed by Yuncheng, Yulin and Dabin who have found that alkylation of carboxylic acids with alkyl halides in the presence of phase transfer catalyst (PTC) can also lead to high yields of esters with 10 minutes irradiation. The reaction of hexanoic acid with benzyl bromide and PTC in a sealed tube gave the ester in good yield (72%)[70].

N-Alkylations also proceed smoothly under microwave conditions; thus irradiation of a mixture of saccharin **69**, alkyl halide **70** on silica gel or alumina leads to the isolation of the product **71** in good yield[71].



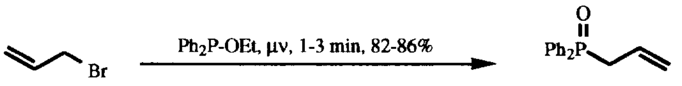
Scheme 51

Villemin has also reported a useful procedure for the preparation of sulphones by microwave assisted alkylation of sodium phenylsulphinate. Thus irradiation of a mixture of the sulphinate and benzyl halide adsorbed onto alumina led to the isolation of the desired product **72** in 40-99% yield. The reaction does appear to have some generality and interestingly the authors report that the reaction with benzyl halide is unsuccessful unless the substrates are adsorbed onto a support[72].



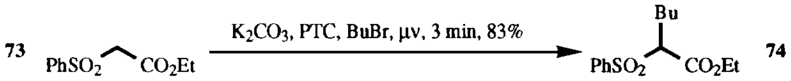
Scheme 52

Giguere and co-workers have reported the rapid and efficient preparation of allyldiphenylphosphine oxide *via* phosphinite allylation. The reaction proceeds satisfactorily by stirring the neat reagents at room temperature overnight but the reaction time can be reduced to one minute using microwave radiation[73] (scheme 53).



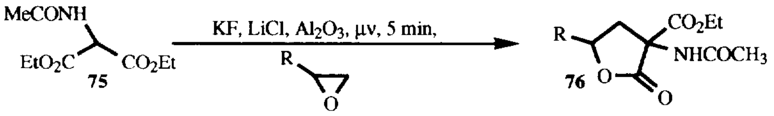
Scheme 53

Alkylation of "active methylenes" has also been successfully carried out using microwave irradiation. Treatment of ethyl phenylsulphonylacetate **73** with alkyl halide in the presence of potassium carbonate and phase transfer catalyst leads to the alkylated product **74** in good yield after 2-3 minutes of microwave irradiation[74].



Scheme 54

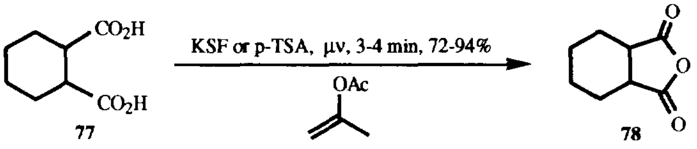
Active methylenes also react with epoxides as illustrated below in the transformation of **75** into lactone **76**[75].



Scheme 55

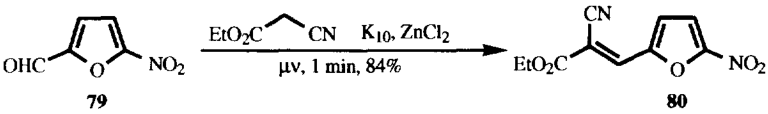
4.2.5. Condensations

The condensation of diacids to anhydrides has been reported by Villemin, Labiad and Loupy as illustrated below in the transformation of **77** to **78**[76].



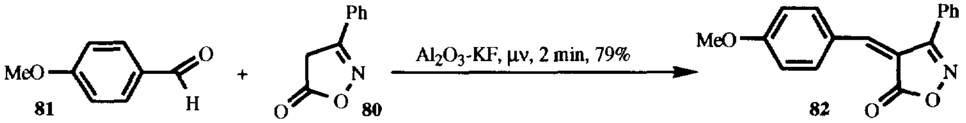
Scheme 56

Clay catalysts have been used to aid microwave assisted condensation of "active methylenes" with aldehydes. Thus condensation of 5-nitro-2-furaldehyde **79** with active methylenes was achieved in high yields by adsorption of the reagents on the Lewis acid K_{10}, $ZnCl_2$ and irradiation with microwaves as illustrated below[77].



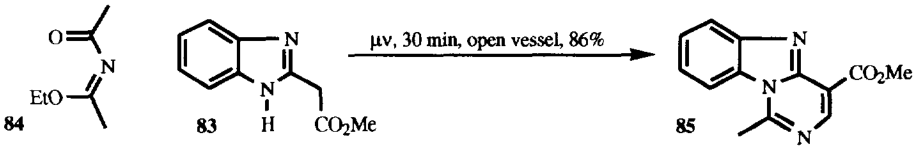
Scheme 57

The Villemin group have reported a range of closely related condensations carried out on Al_2O_3-KF as exemplified in the condensation of **80** with aldehyde **81** to give **82** (open vessel, 2-15 minutes µv, 71-92%)[78].



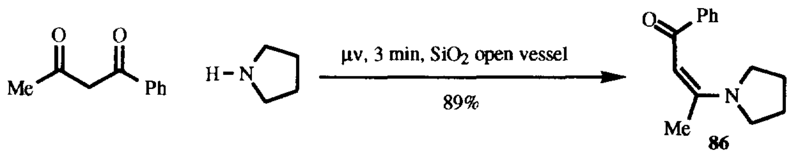
Scheme 58

A microwave assisted cyclocondensation approach to pyrimido[1,6-a]benzimidazoles has also been developed. Irradiation of neat benzimidazole **83** and *n*-acylimidate **84** in an open vessel leads to a good yield of product **85** *via* a condensation involving a conjugate addition-elimination, condensation sequence. The use of an open vessel allows the vapourisation of the ethanol and water produced in the reaction[79].



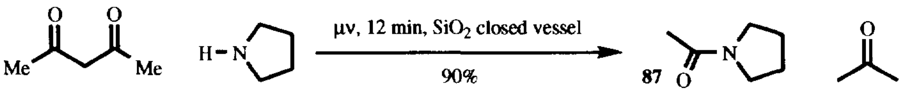
Scheme 59

The formation of enaminoketones has recently been reported by Hamelin and co-workers[80]. Microwave irradiation of a β-diketone with an amine leads to the enaminoketone **86** as exemplified below in scheme 60.



Scheme 60

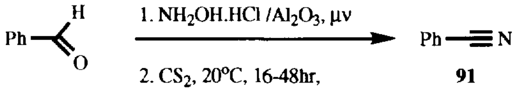
The procedure involves supporting the reagents on silica gel or clay K_{10} interestingly in some cases if the reaction is carried out in a sealed vessel the amide is formed as illustrated below.



Scheme 61

The authors propose that in the closed vessel the water of condensation hydrolyses the enaminoketone **86** to give **87**. If the transformation is carried out in a closed vessel with dried silica gel, only traces of hydrolysis product **87** are identified.

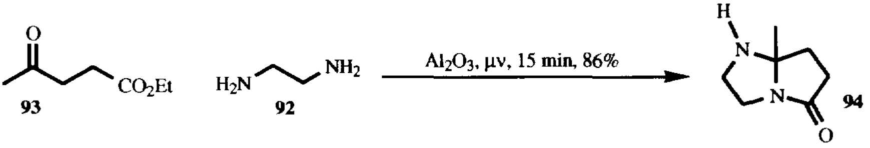
Villemin and co-workers have described the transformation of aldehydes to nitriles[81], thus irradiation of benzaldehyde with hydroxylamine hydrochloride on alumina followed by treatment with CS_2 at room temperature leads to the nitrile **91** in 89% yield.



Scheme 62

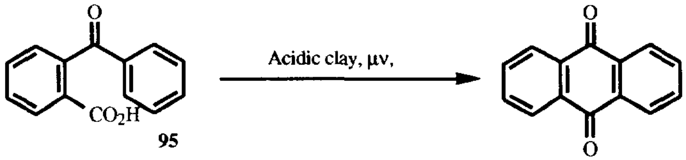
The same overall transformation has also been reported by Alvarez and co-workers who isolated moderate to good yields of nitriles by microwave irradiation of the appropriate aldehyde, hydroxylamine hydrochloride and Mexican bentonite[82].

Microwave assisted cyclocondensations can be used to prepare heterobicycles as illustrated below. Irradiation of diamine **92** with keto-ester **93** led to the isolation of product **94** in 86% yield. The reaction was carried out by supporting the reagents onto alumina and irradiating in an open vessel[83].



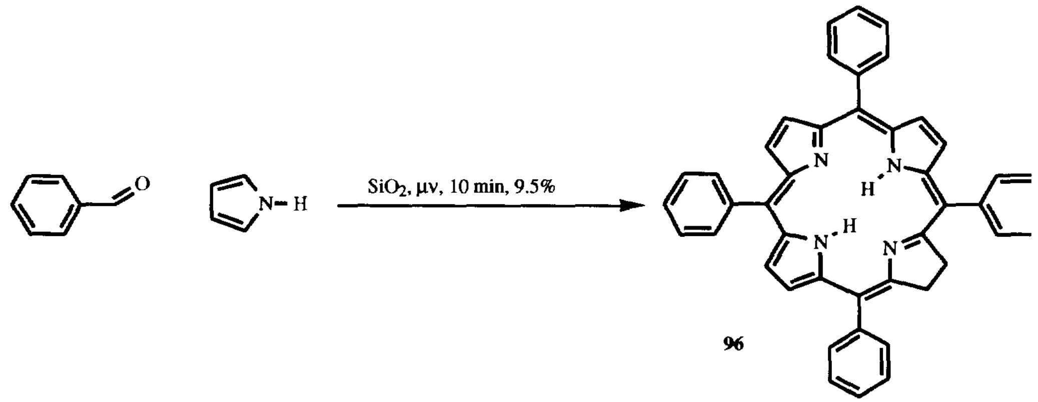
Scheme 63

The application of microwaves to the industrially important raw material anthraquinone has been investigated[84]. It has been found that microwave assisted acid catalysed cyclodehydration of **95** could be carried out using the same batch of catalyst without a reduction in yields (12 reactions) whereas using conventional heating the yield was around 50% after four reactions using the same batch of catalyst.



Scheme 64

An impressive microwave assisted cyclocondensation has been used to prepare tetrapyrroles as illustrated in the synthesis of **96** shown below. Detailed investigations enabled the group to optimise the process at c.a. 10% and although the yield is modest, purification and isolation of the product is reasonably simple[85].



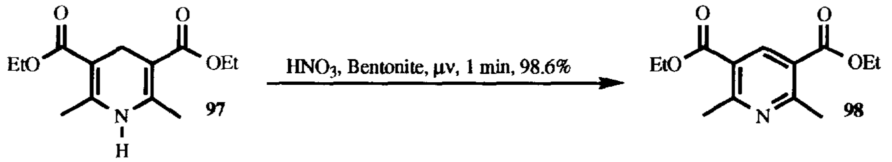
Scheme 65

4.2.6. *Peptide Synthesis*

In a potentially very exciting development Wang and co-workers have described microwave assisted solid phase peptide synthesis[86]. They report that coupling of Fmoc-protected amino acids using either symmetrical anhydride or active ester methodology can be carried out under microwave conditions with a significant reduction in reaction time (2-6 minutes) compared to conventional procedures. Analysis shows that the coupling reactions proceed in high yield with no apparent racemisation and given the opportunities which exist for automation this could find extensive utilisation in the rapid synthesis of peptides and proteins.

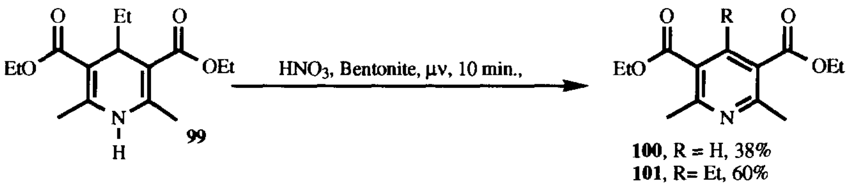
4.2.7. *Oxidation*

Alvarez and co-workers have reported a highly efficient aromatisation process as illustrated below in the transformation of **97** to **98**[87].



Scheme 66

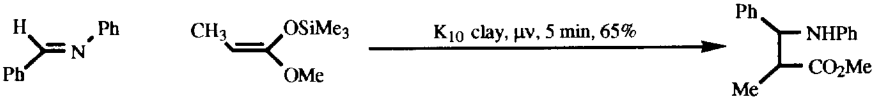
It is known that if an electron releasing substituent is present at the 4 position, oxidation can proceed with concomitant dealkylation. These same workers have found that, in contrast with conventionally promoted dihydropyridine oxidations, 4 alkyl substituted dihydropyridines give a mixture of products as illustrated in the oxidation of **99** to **100** and **101**[88].



Scheme 67

4.2.8. *Silicon*

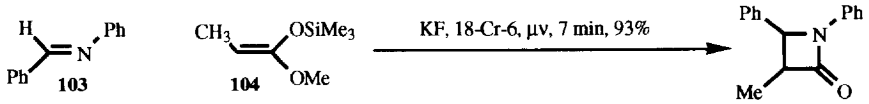
Texier-Boullet, Latouche and Hamelin have explored the reaction of silyl ketene acetals with imines under microwave irradiation[89]. The versatility of the microwave assisted approach is nicely illustrated, when the reactions are carried out by adsorption of the reagents onto K_{10} montmorillonite clay the addition product **102** is isolated as illustrated in scheme 68.



102

Scheme 68

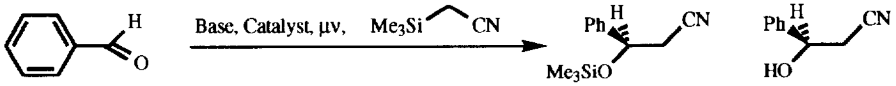
When the reaction is carried out by mixing the neat reagents with 18-crown-6 and irradiation in a closed vessel, β-lactams were isolated in moderate to good yields as illustrated below in the transformation of **103** and **104** to **105**.



103 **104** **105**

Scheme 69

In another class of reaction involving a silicon containing nucleophile, the same group have extensively investigated some synthetically useful silyl-Reformatsky processes. They have found that a range of both supported and unsupported reaction conditions (alkali metal fluorides/ Al_2O_3, MgO or clay) can be used to prepare useful addition products as shown below[90,91] in scheme 70.



Scheme 70

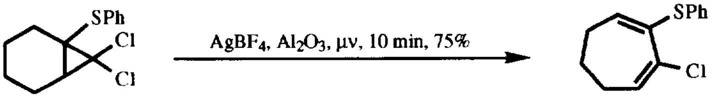
4.2.9. *Rearrangements*

Several groups have described microwave assisted pinacol rearrangements, for example irradiation of **105** with Al^{3+}-Montmorillonite (15 minutes) gave the rearranged product **106** in good yield (99%). Similar yields could be obtained using conventional heating, however reaction times were significantly longer (15hrs)[92].

105 **106**

Scheme 71

Villemin and Labiad have examined an interesting ring expansion process illustrated below, although the process could be achieved by heating the reagents at reflux in methanol the authors report that by carrying out the reaction under dry supported conditions a more efficient transformation was achieved[93] as depicted in scheme 72.

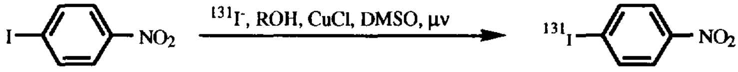


Scheme 72

5. The Microwave Effect

There is some significant level of controversy surrounding the nature of the effects of microwaves on organic reactions. It is clear that when irradiating organic materials in a microwave oven the frequency of the radiation (2.45GHz) does not "activate" specific bonds in a molecule. Given therefore that the coupling of microwaves with the dipolar molecule leads to a dielectric heating effect, it has been argued that this form of heating will not lead to any kinetic differences compared to any other form of heating[94-96]. Thus some of the early reports[97] claiming specific microwave effects have been discounted as merely thermal effects[94,98] and it is likely that many examples of "rate enhancements" can be attributed to the heating of solvents above their boiling points[23]. The problems associated with comparison of microwave assisted reactions with conventionally heated "controls" become apparent in this context; it is difficult to accurately measure the internal temperature and microwave thermolysis may give an uneven heat distribution. It has also been suggested that under certain circumstances (particularly under heterogeneous reaction conditions using solid supported metal catalysts[15]) there may be the possibility of producing hot spots[99]. Thus, it is still not clear whether specific microwave effects exist, however the simple observation that a variety of reactions can be carried out rapidly under microwave conditions (and sometimes with improved associated yields) is of significant environmental and commercial value. The more efficient heating associated with microwave thermolyses reduces reaction times and therefore electricity costs; the efficiency of microwave assisted solid state reactions may help to minimise the production of waste solvent and in general microwave assisted reactions may lend themselves to automation[100]. This technology has been of value in the preparation of radiopharmaceuticals[101]; it has been shown that the reduction in reaction time can lead to improved radiochemical yields and a reduction in human exposure to radiation. Welch and co-workers have successfully investigated this methodology and compared conventional and microwave assisted synthesis of fluoro and iodo aromatic compounds using nucleophilic substitution reactions. In one of the reported examples, treatment of iodide **107** with $^{131}I^-$ gave the labelled product **108** in 80% yield in 60 seconds (scheme 73).

107



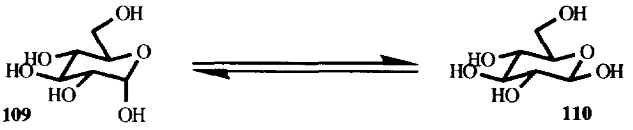
108

Scheme 73

The authors also examine the preparation of ^{11}C labelled compounds using a reductive amination approach which could also be improved using microwave heating. It is likely that microwave technology will continue to aid in the preparation of labelled organic compounds.

However the most exciting and perhaps the most important developments would be those associated with non-thermal effects specific to microwave assisted reactions; whilst it is arguable whether such effects have been convincingly demonstrated there have been some interesting observations.

Pagnotta and co-workers examined the microwave assisted mutarotation of α-D-glucose **109** to **110** in a range of solvents[102] (scheme 74).

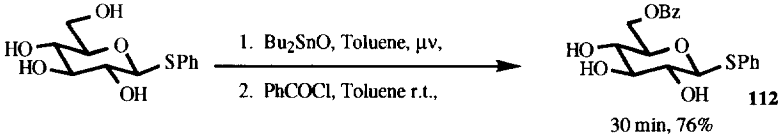


109 **110**

Scheme 74

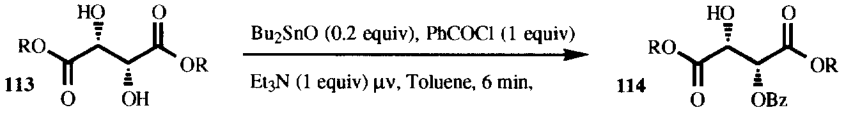
It was found that the ratio of **109** to **110** reached approximately 1:1 more rapidly using microwave thermolyses than the conventionally heated control. However most interestingly it was found that microwave thermolysis in a particular solvent mixture ($EtOH:H_2O$, 1:1) led to a change in equilibrium distribution in which a greater proportion of **109** was present.

In another interesting example Herradon and co-workers have developed a microwave assisted selective benzoylation reaction catalysed by di-*n*-butyltin oxide[103]. Prior to this report it was known that dibutylstannylene acetals could be benzoylated to give moderate to good yields of monobenzoylated products e.g. **112**. The formation of the acetals under conventional conditions requires heating of a diol with di-*n*-butyltin oxide for several hours; this time can be significantly reduced using microwave technology.



Scheme 75

What is most noteworthy about this report is the development of a catalytic process; because the benzoylation reaction is faster than acetal formation under conventional heating conditions, the use of catalytic di-*n*-butyltin oxide in the presence of base leads to the formation of products *via* non-selective benzoylation. However by enhancing the acetal formation under microwave conditions, a catalytic quantity of di-*n*-butyltin oxide and stoichiometric base can be used to give a synthetically useful selective benzoylation procedure as exemplified below in the formation of **114** from **113**. It would appear that the formation of the di-*n*-butylstannylene acetal competes with the non-tin mediated benzoylation under microwave conditions. The authors demonstrate this by repetition of the reaction but in the absence of di-*n*-butyltin oxide; only 14% product and 60% starting diol are isolated under these conditions.



Scheme 76

Stuerga and co-workers have illustrated a useful benefit of utilising microwave irradiation to assist very fast reactions[104]. They analyze microwave assisted sulphonation of naphthalene which had been previously reported by Abramowitch[11,14] and claim that they can control the regioselectivity of the substitution process by simply moderating the microwave power level. Thus at high power levels a greater proportion of the 2-isomer is observed whereas at lower power levels a significant proportion of the 1-isomer is produced. It is suggested that it is the effect of heating rate on the reaction which leads to this selectivity. The authors also suggest that there may be other cases in which product distributions may be affected by heating rates and thus heating source.

6. Concluding Remarks

There is no doubt that microwaves can be used to great effect in organic synthesis; the "in situ" generation of heat is very efficient and can be used to significantly reduce reaction times of numerous synthetically useful organic transformations. Thus microwave assisted organic synthesis has advantages over conventional technology: it is more energy efficient and it can lead to improved isolated yields of products (if thermal decomposition is associated with the conventionally heated reactions). The possibilities for automation are clear and the opportunities for executing numerous reactions at the same time in the same microwave cavity is attractive if large numbers of compounds need to be prepared rapidly. The obvious application of this approach to combinatorial synthesis should provide a major impetus for further developments in this area; a particularly important feature will be the continued development of microwave assisted solid phase reactions. The effects of microwave radiation on chemo-, regio- and stereoselectivity in synthesis and the continued quest for evidence of a non-thermal microwave effect are also important aspects which need to be addressed. It is clear that microwave assisted synthesis, whilst still at an early stage of development, has much to offer synthetic chemists. It is likely that, with increased activity in this exciting area, widespread acceptance of this technology will result in the microwave oven becoming an integral part of every modern organic synthesis laboratory.

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