Microwave irradiation: more than just a method for accelerating reactions

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Reviewing the literature published up to December 1996

1 Introduction

Microwave radiation is a non-conventional energy source whose popularity and synthetic utility in organic chemistry have increased considerably in recent years.[1] Characteristically, microwaves generate rapid intense heating of polar substances with consequent significant reductions in reaction times, and give cleaner reactions that are easier to work up than those from conventional heating, and in many cases give higher yields. However, although important, these are not the only advantages offered by the technique.[2]

In the early days of microwave irradiation, reactions were performed in domestic ovens. The development of new equipment which allows focused irradiation and power and temperature control has now led to safer reactions which can be scaled up without the need to modify experimental conditions.[3]

With microwaves, the heating is created in the interior of the sample and is then radiated outward. This is in contrast with conventional heating, where the heat is generated in the outer region and must then be directed towards the centre. This, coupled with the shorter reaction times, implies a vast improvement in operations like distillation, and considerable savings in energy, a feature which takes on greater importance at process development level in the chemical industry.

Unlike other non-conventional energy sources (such as ultrasound, high pressure or vacuum flash thermolysis), microwaves lend themselves easily to industrial use, where they provide many advantages in certain production processes.

Finally, the synergy of this methodology with reactions performed on support media and/or in the absence of solvent[4] constitutes an environmentally clean technique which avoids the generation of highly contaminating residues, like organic solvents and mineral acids, and which allows the attainment of high yields of products at reduced energy costs.

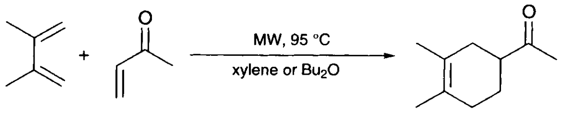
The aim of this review is not to compile a list of examples of the synthetic applications of microwave irradiation in which only better yields and reduced reaction times have been achieved, since several such reviews already exist.[1-5] Rather, the aim is to summarise the current status of the 'microwave effect' by bringing together articles which argue both for and against the existence of such an effect. Accordingly, the literature has been reviewed wherein microwaves have been shown to be essential for reactions to proceed, and where microwave radiation has resulted in chemo-, regio- or stereoselectivities different from those obtained by conventional heating.

2 The issue of a specific 'microwave effect'

The existence of results which cannot be explained solely as a consequence of rapid heating has led various authors to postulate a so-called 'microwave effect'. Hence, acceleration or changes in reactivity and selectivity in reactions can be explained by a specific radiation effect and not merely by a thermal effect.

Jacob *et al.*[6] have published an excellent review on synthetic results which have been attributed to the microwave effect, and various authors have proposed that changes in thermodynamic parameters under microwave irradiation are the cause of the effect. Nevertheless, some of these theories have been subsequently put in doubt by other authors and indeed by the same authors themselves.

Berlan *et al.*[7] found that in cycloaddition reactions performed in xylene or dibutyl ether (**Scheme 1**), the rates were always faster under microwave conditions. The observed accelerations were more significant in apolar solvents which showed weak dielectric losses (**Fig. 1**). Because of this, the authors have proposed that a modification to $\Delta G^{\ddagger}$ is produced, possibly through a change in the entropy of the system. They have also suggested the existence of 'hot spots', analogous to those described for ultrasound chemistry.[8] Subsequently, Strauss *et al.*[9] showed that the kinetics of these and other reactions are similar under microwave irradiation and classical heating, indicating that there was no specific effect.



Scheme 1

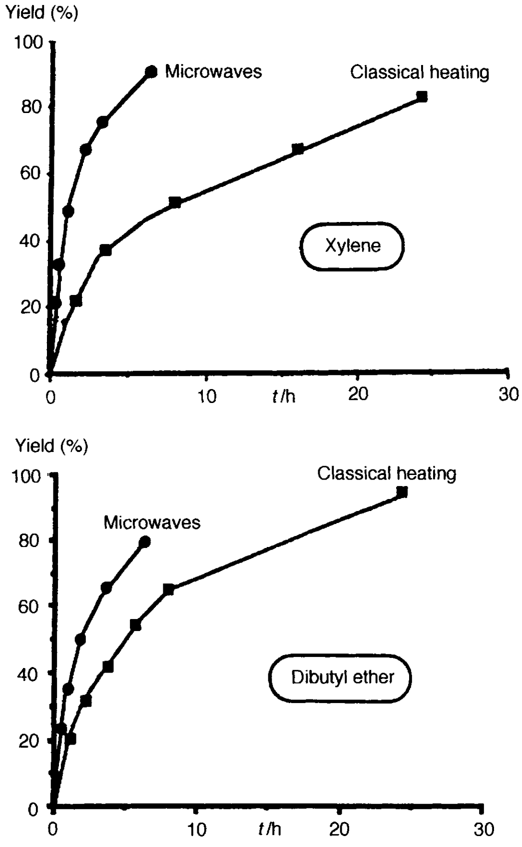
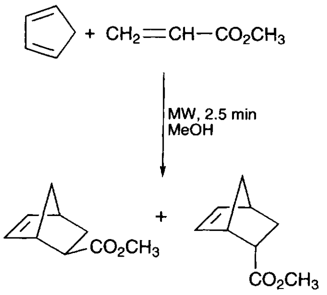


Fig. 1 Yield = f(t) for reaction depicted in **Scheme 1** at 95 °C (Reproduced with permission from ref. 2, J. Berlan, P. Giboreau, S. Lefeuvre and C. Marchand, *Tetrahedron Lett.*, 1991, **32**, 2363; copyright Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, UK OX5 1GB)

Coinciding results in the cycloaddition between cyclopentadiene and methyl acrylate have been described by Gedye *et al.*[10] (**Scheme 2**). Microwave radiation does not alter the *endo*/*exo* selectivity in this reaction, and the changes which are observed can be explained by the fact that the reactions under microwave conditions occur at higher temperatures than those taking place at reflux. Likewise, Bond[11] and Strauss[12] and their collaborators showed that in esterification reactions performed in carefully controlled systems, the reaction rates are identical in the presence or absence of microwave radiation and that the final yields depend only on the temperature profile and not on the mode of heating.



Scheme 2

Jahngen and co-workers[13] have shown that the rate of hydrolysis of ATP is 25 times faster under microwave irradiation than under classical heating at comparable temperatures. The authors attributed this fact to the direct absorption of radiation or to selective excitation of the water of hydration over the bulk solution. They pointed out that spectroscopic heating (by microwaves) can increase the kinetic energy of the solvent through direct absorption of the irradiated energy. Subsequently, the authors showed that the rate of hydrolysis depends solely on the temperature and not on the method of heating.[14]

In this respect, both Berlan *et al.*[15] as well as Strauss *et al.*[3] ruled out the possibility that microwave radiation can excite rotational transitions. When a compound absorbs microwaves the dielectric heating causes an increase in the temperature of the system. When the internal energy of the system is raised it is distributed among translational, rotational or vibrational energies independently of the mode of heating. Consequently, it was concluded that no kinetic differences should be expected between reactions heated by microwaves and those heated by conventional means if the temperature is known and the solution is thermally homogeneous. Molecular agitation and mobility have also been factors used to explain the effects attributed to microwave radiation.

Recently the thermal decomposition of sodium hydrogen carbonate has been studied (**Scheme 3**).[16] The authors found that the activation energy of the reaction is reduced by microwave radiation (**Fig. 2**). Given that temperature control is crucial in these experiments, the authors endeavoured to ensure the reliability of the temperature determination both in the spatial and time domain. Although the mechanism is not well understood, the application of a microwave field to dielectric materials induces rapid rotation of the polarised dipoles in the molecules. This, in turn, generates heat due to friction while simultaneously increasing the probability of contact between molecules and atoms, and enhancing the reaction rate and reducing the activation energy.

$$2\,NaHCO_3 \longrightarrow Na_2CO_3 + H_2O + CO_2$$

Scheme 3

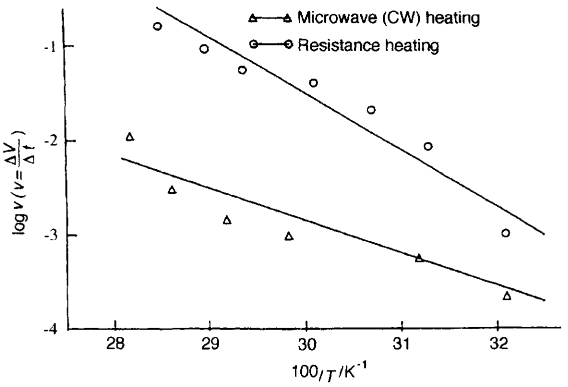


Fig. 2 Arrhenius' plot of $NaHCO_3$ solution
(Reproduced by permission from ref.16)

However, after studying the synthesis of titanium carbide Binner *et al.*[17] concluded that molecular mobility can increase in the presence of a microwave field and that in this case it is the Arrhenius pre-exponential factor A which changes and not the energy of activation [see eqns. (1) and (2)], where

$$K = A\mathrm{e}^{-\Delta G/RT} \qquad (1)$$

$$A = \gamma\lambda^2\Gamma \qquad (2)$$

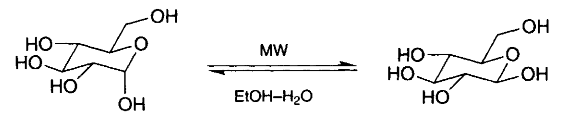
γ = geometric factor which includes the number of nearest-neighbour jump sites, λ = distance between different adjacent lattice planes (jump distance) and Γ = jump frequency].

An increase by a factor of 3.3 in the Arrhenius pre-exponential factor could explain the acceleration in reaction rate with microwaves. The Arrhenius pre-exponential factor depends on the frequency of vibration of the atoms at the reaction interface, and because of this it is proposed that it can be affected by a microwave field.

The use of microwaves leads to a temperature reduction of 80–100 °C in the sintering temperature of partially stabilised zirconia,[18] an effect which is of a non-thermal nature. Wroe and Rowley[18] have shown that a microwave field improves either the volume or grain-boundary mechanism, rather than improving diffusion at the surface, which is dominant at low temperatures. Microwaves preferentially increase the flux of vacancies within grain boundaries in the sample.

A kinetic study on the heterogeneous phase reduction of soybean oil[19] with ammonium formate has shown that the rate of hydrogenation is eight times greater under microwave conditions than under classical conditions at the same temperature. The effect observed can be attributed not to temperature or pressure effects, but to the fact that microwave heating must assist the transport process at the catalyst–oil–water interface.

In a study of the mutarotation of α-D-glucose **1** to β-D-glucose **2** (**Scheme 4**), it was found that in $EtOH-H_2O$ 1:1, apart from a more rapid equilibration with microwaves over conventional heating, microwaves led to a modification of the equilibrium position such that a greater amount of the α-D-glucose was obtained than would be attained under classical heating (Figure 3).[20] This extraordinary effect cannot be explained by a classical heating effect and is the most obvious example of a possible specific action created by a microwave radiation field.



1 **2**

Scheme 4

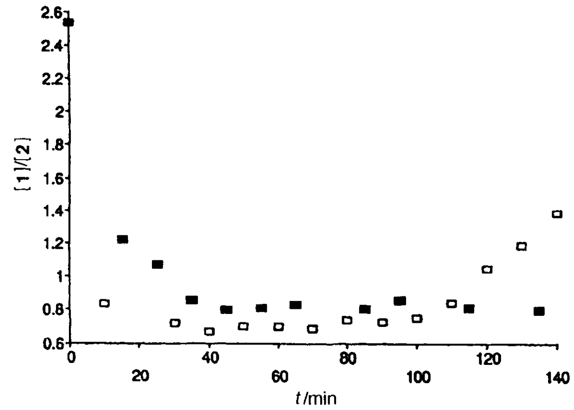


Fig. 3 Ratio of **1** to **2** (α-D-glucose to β-D-glucose) *vs* time for (■) conventionally heated and (□) microwave-heated reaction (Reproduced with permission from ref. 20; copyright John Wiley & Sons Ltd.)

3 Presence of 'hot spots'. False microwave effects?

Several researchers have detected or postulated the presence of 'hot spots' in samples irradiated with microwaves. This effect, which is related to that observed with ultrasound,[8] arises as a consequence of the inhomogeneity of the applied field, implying that in certain zones within the sample the temperature is much greater than the macroscopic temperature, and hence this is not representative of the reaction conditions as a whole. This is a thermal effect and so has been described as the 'false microwave effect'.

Baghurst and Mingos[21] have detected an overheating effect in polar liquids using microwaves, where overheating to between 13–26 °C above the normal boiling point may occur (**Fig. 4**). This effect can be explained by the 'inverted heat transfer' effect (from the irradiated medium towards the exterior) since boiling nuclei are formed at the surface of the liquid and could explain the enhancement in reaction rates observed in organic and organometallic chemistry.

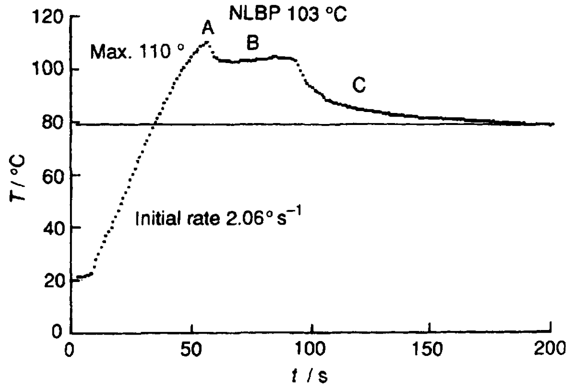
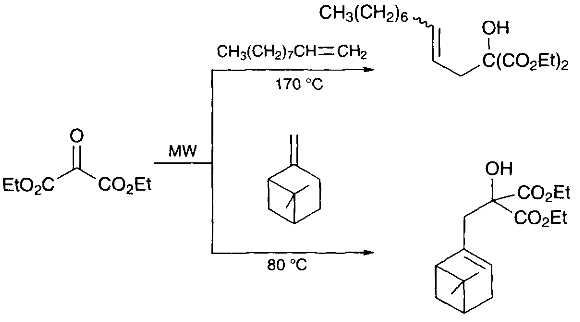


Fig. 4 Microwave heating of ethanol (Reproduced from ref. 21)

Berlan *et al.*[15] demonstrated that ene reactions of various enophiles (**Scheme 5**) showed that neither reaction rates nor product distributions were affected by microwave radiation in homogeneous conditions. They detected hot spots and they stated that the macroscopic (bulk) temperature was not representative of the true reaction conditions. Subsequently, they showed that the field intensity is not homogeneous in liquids and that it greatly depends on the nature of the solvent and the temperature.[22] This observed power heterogeneity changes with time and induces the formation of hot and cold zones in the medium. Since the response of the temperature probe is very slow in relation to this heterogeneity, the measured temperature is an average value, and hence it is necessary to reflect on the significance of the measured temperature in this type of reaction. A rise in power leads to greater heterogeneity in the reactor and poorer reproducibility.



Scheme 5

Finally, these authors have studied the microwave effect on the hydrolysis of nitriles under heterogeneous conditions.[23] They observed that the acid–amide selectivity remains constant under microwaves but diminishes using classical heating since the acid degrades more quickly in these conditions. The effect was ascribed to the presence of hot spots excluding any molecular activation effect or step by step accumulation of energy in order to reach the transition state. A further advantage of microwave heating in these type of reactions is the absence of inertia. Heating terminates when the equipment is turned off which means cooling is much faster.

Suard *et al.*[24] have considered two important differences between conventional heating and microwave radiation. First, under microwave irradiation, the initial slope of the plot of sample temperature against time is not zero, and in contrast to conventional heating, conduction flow represents the major flow of the system. In consequence, a rapid heating must be responsible for the observed effects.

Stuerga *et al.*[25] have supported the presence of hot spots. In order to determine the presence of a microwave effect they considered it necessary to study reactions in which reaction time is of the same order as the heating time. Hence they have studied the sulfonation of naphthalene to give -1- and -2-naphthalene sulfonic acids. The 1-/2- selectivity differs depending on the irradiation power. The origin of this selectivity change is found in the variation in the heating rate caused by the change in irradiation power. The authors therefore considered that microwave heating might be a useful method for achieving heating rates and thermal gradients not accessible by conventional heating. These new conditions can lead to modifications or inversions of selectivities in certain reactions.

Non-thermal effects can be generated through localised overheating and sometimes these are due to problems related to temperature estimation, in particular local thermal gradients induced by microwave heating.[26]

Finally, the presence of hot spots is also supported by the work of Strauss and Trainor. Their studies on reaction rates showed that in homogeneous media the reaction rate was the same using either microwaves or classical heating. Generally speaking, the technical difficulties, especially in temperature measurement, are responsible for the inconsistencies described.

On the other hand, heterogeneous systems are more difficult to study properly and the presence of 'hot spots' is most likely due to the heterogeneity of the medium.

Temperature determination of the sample in microwave systems is complex and is one of the reasons for the lack of reproducibility in some reactions and for the controversies over the 'microwave effect'. The methods employed vary, ranging from the exclusive determination of the sample temperature once irradiation has been finished, or placing capillaries containing substances of known melting points in the oven, to the use of optical fibre sensors or infrared thermography. This last method is the most widely used at present and gives reproducible results.

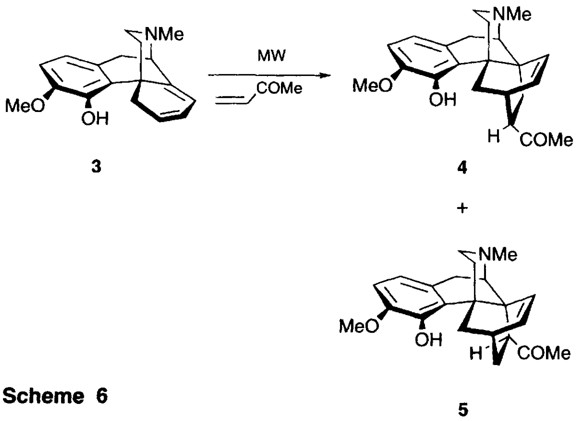
Although the existence of the so-called 'microwave effect' has not been proved, the utility of microwaves in improving several processes or in modifying chemo-, regio- or stereo-selectivity is apparent. These changes seem to arise in many cases from the heating rate provided by microwaves, inaccessible using classical heating. However, there are some results which cannot be rationalised simply in terms of the rapid heating effect, for example the effects on mutarotation described earlier.[20] Finally, it does seem to have been demonstrated that microwaves cause an increase in molecular mobility, although there is no general consensus as to the effect it has in the thermodynamic equation, be it due to a variation in the activation free energy or in the Arrhenius pre-exponential factor A.

The examples collected in this review have been grouped in two categories: (a) reactions in which microwaves produce a dramatic improvement in the process and (b) reactions in which microwaves produce a modification in chemo-, regio- and stereo-selectivity.

4 Process improvements

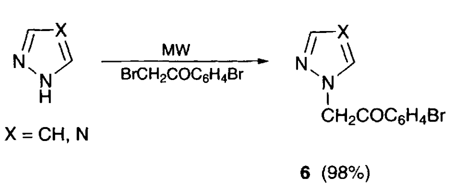
The beneficial effects of microwave radiation can be utilised to improve processes, especially if classical methods require harsh conditions, prolonged reaction times or high temperatures. Where processes involve sensitive reagents or where an increase in reaction temperature could cause product decomposition, microwave radiation can also be used to advantage.

In one of the pioneering publications on microwave activation, Linders *et al.*[27] examined the cycloaddition of 6-demethoxy-β-dihydrothebaine **3** with methyl vinyl ketone (**Scheme 6**). Whereas classical heating caused extensive polymerisation of the dienophile, a 3:2 mixture (32%) of the two cycloadduct isomers **4** and **5** was obtained under microwave conditions.



Scheme 6

Loupy *et al.*[28] have applied a combination of the absence of solvent with microwave irradiation in order to prepare 1-(4-bromophenacyl)azoles **6** (**Scheme 7**). The reaction does not occur under normal heating and the authors have rationalised the result in terms of a specific non-thermal effect caused by the microwaves.



Scheme 7

Recently, the N-alkylation of aniline with propan-1-ol and catalytic amounts of Raney nickel under microwave irradiation has been described, and yields were excellent (91%).[29] Again the failure to give any reaction after 24 h at the same temperature in the absence of microwaves suggests a non-thermal effect in the reaction.

The selective O-alkylation of amido alcohols **7** has also been described using microwave irradiation on alumina (**Scheme 8**).[30] While the reaction leading to **8** is slow at room temperature, resulting in large percentages of polyalkylated products, conventional heating leads to decomposition. With microwave irradiation selective O-alkylation is achieved in high yield.

$\mathrm{CF_3CONHCH_2CH_2OH}$

7

$$\Big\downarrow\ \begin{array}{l}\text{MW}\\ \mathrm{CH_2{=}CHCH_2Br{-}Al_2O_3}\end{array}$$

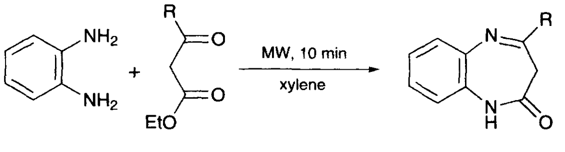
$\mathrm{CF_3CONHCH_2CH_2OCH_2CH{=}CH_2}$

8

room temp.	7 d	18%
MW	20 min	52%

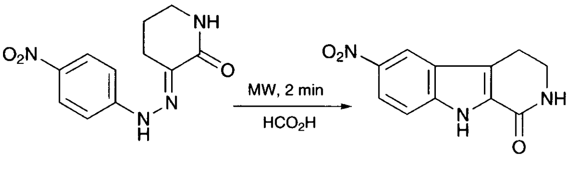
Scheme 8

Soufiaoui[31] has prepared benzodiazepin-2-ones **9** (82–98%) by condensing o-phenylenediamines with β-keto esters in xylene under microwave irradiation in a conventional microwave oven for 10 min (**Scheme 9**). Applying an analogous treatment using normal heating failed to give any product. Other diazepines[32] have recently been prepared by microwave activation.



Scheme 9 **9**

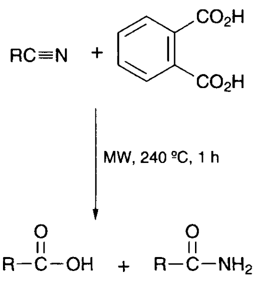
The Fischer cyclisation of piperidine-2,3-dione 3-p-nitrophenylhydrazone **10** with formic acid, leading to the corresponding β-carboline **11**[33], occurs in 72% yield under microwave irradiation (**Scheme 10**). Classical heating was found to be ineffective for this reaction.



10 **11**

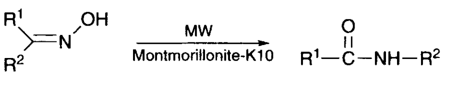
Scheme 10

The hydrolysis of nitriles in dry media has been performed by heating a mixture of the nitrile and phthalic acid under pressure (**Scheme 11**).[23] The reaction gives rise to a mixture of the corresponding amides and carboxylic acids both under classical heating and microwave conditions. However, at high temperatures, recovery of the product, especially the carboxylic acid, is much lower when employing the classical heating method due to decarboxylation of the product, something which does not occur with microwaves.



Scheme 11

Langa *et al.*[34] have studied the Beckmann rearrangement of oximes with montmorillonite as support as well as acid catalyst (**Scheme 12**). Employing microwaves prevented hydrolysis of the oxime to the corresponding carbonyl compound. Moreover, the reaction occurs with poorly reactive oximes which do not react under classical conditions.



Scheme 12

The oxidation of benzylic and allylic alcohols **12** to aldehydes with MnO_2/bentonite under microwave irradiation takes place in 1 min with yields of 32–100%,[35] yields of only around 3% being obtained with classical heating (**Scheme 13**). This result has been attributed to a specific non-thermal effect.

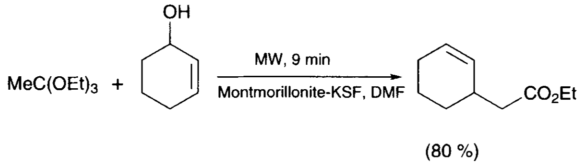
$$\mathrm{RCH_2OH} + \mathrm{MnO_2} \xrightarrow{\text{MW, 1 min}} \mathrm{RCHO}$$

R = aryl, vinyl

12

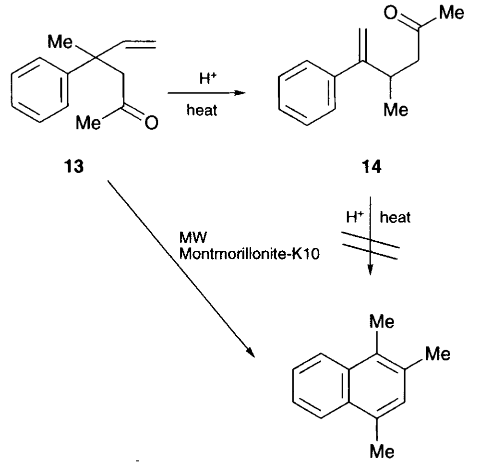
Scheme 13

The Claisen rearrangement of a series of allylic alcohols and triethyl orthoacetate in the absence of solvent with microwaves and montmorillonite–KSF catalyst takes place in yields of 66–100% (**Scheme 14**); the reaction does not take place under normal heating.[36]



Scheme 14

Another example of the modification of reactivity that can been seen with microwave radiation involves the enone **13** as starting material.[37] Thus, in an acid medium under normal heating, isomerisation of **13** to the enone **14** takes place, while under microwave radiation the reaction proceeds further until the formation of naphthalene derivative **15** (**Scheme 15**).

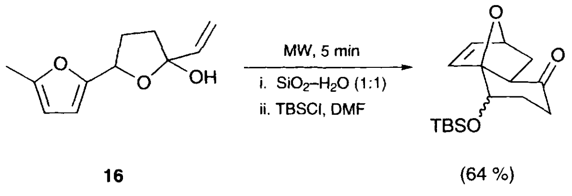


Scheme 15

15

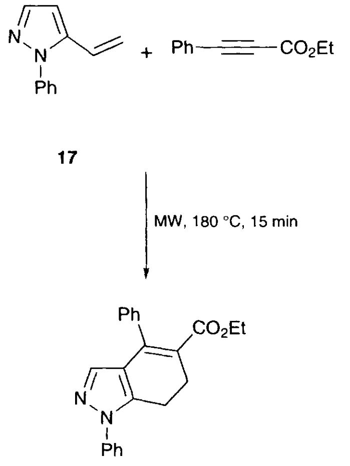
The reaction of *O*-silyl ketene acetals with aldimines leads to β-lactams in yields that vary between 47 and 98%.[38] Under classical heating however, the yields are never greater than 30% and mixtures of the β-lactam and the corresponding β-amino ester are frequently obtained.

The intramolecular Diels–Alder reaction involving the hemiacetal **16** fails under normal thermal treatment.[39] However, the reaction has been successfully carried out in 64% yield by using microwaves and absorbing the product onto silica gel/water (**Scheme 16**).



Scheme 16

More recently, Diaz-Ortiz *et al.*[40a] have described the Diels–Alder cycloadditions of 4- and 5-vinylpyrazoles **17** to various poorly reactive dienophiles (**Scheme 17**). Under classical conditions the cycloadditions either do not take place at all or occur in very low yields on account of competing polymerisation of the vinylpyrazoles.[40b] Microwave heating, however, with its consequent rapid heating, results in an increase in the rate of cycloaddition.



Scheme 17

The conversion of benzylic alcohols into benzylic iodides has been achieved by microwave irradiation using Montmorillonite-KSF in yields which vary between 55 and 90% (**Scheme 18**).[41] After 8 h heating under reflux in DMF no reaction is seen to take place.

$$\mathrm{ArCH_2OH + NaI} \xrightarrow[\text{Montmorillonite-KSF}]{\text{MW, 5 min}} \mathrm{ArCH_2I}$$

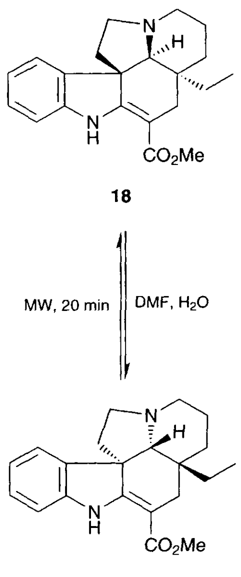
Scheme 18

An interesting application of microwave activation is the racemisation of optically active compounds. A wide range of amino acids has been racemised quantitatively within two minutes (**Table 1**), avoiding considerable decomposition associated with the use of classical heating.[42]

Table 1 Racemisation of optically active amino acids under microwave irradiation ($t = 120$ s)

Amino acid	Optical purity of product (%)	Yield (%)
L-Ala	0	100
L-Arg	2	100
L-His	0	95
L-Met	0	98
L-Val	0	100
L-Tyr	0	93

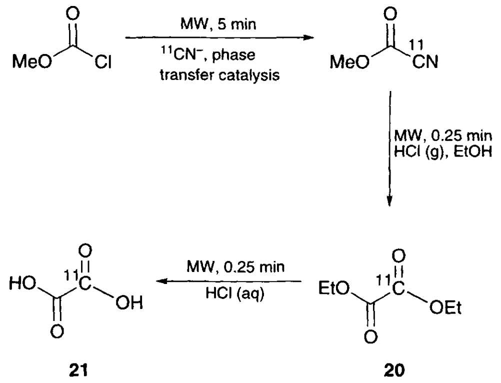
Likewise, complete racemisation of (−)-vincadifformine **18**[43] is achieved in two consecutive Diels–Alder cycloreversion and cycloaddition steps by irradiating in DMF over 20 min (**Scheme 19**). The (+) isomer **19** is of use in the preparation of the alkaloid vincamine which is widely used as a drug. Classical racemisation requires prolonged refluxing and, as in the previous case, is accompanied by a significant amount of decomposition products.



Scheme 19

The acceleration effect, and hence the extremely short reaction times associated with microwave conditions, allows short-lived compounds to be synthesised which otherwise could not be made by classical means. Thus, one interesting application of activation by microwaves is the preparation of isotopically labelled drugs of short half-life (^{11}C,

$t_{1/2}=20$ min; ^{122}I, $t_{1/2}=3.6$ min and ^{18}F, $t_{1/2}=100$ min). The technique has been successful in reducing reaction times by a factor of 20 and in doubling the radioactivity of the final product.[44] Thus, for example, Stone-Elander *et al.*[44b] have described the preparation of [^{11}C]diethyl oxalate **20** and [^{11}C]oxalic acid **21** with microwaves (**Scheme 20**), in which they managed to reduce the reaction time with respect to that of classical conditions. These products have been utilised in the preparation of 2,3-dihydroxyquinoxaline, the basic structural unit in antagonists of the receptor systems of certain amino acids.



Scheme 20

5 Modifications in selectivity

In the sulfonation of naphthalene with microwaves, Stuerga *et al.*[25] showed that selectivity could be modified depending on the power applied. In the case of competing reactions, one could suppose that by controlling the rate of heating, one reaction could be favoured over the other. If we consider a kinetic model based on Arrhenius' Law, for two competitive reactions such as those shown in the scheme below, an increase in heating rate together with a reduction in reaction time allows two special situations to be envisaged:

$$R_1 + R_2 \underset{k_2,\,E_2}{\overset{k_1,\,E_1}{\rightleftharpoons}} P_1 \qquad (3)$$

$$R_1 + R_3 \underset{k_4,\,E_4}{\overset{k_3,\,E_3}{\rightleftharpoons}} P_2 \qquad (4)$$

The first situation is so-called induced selectivity, described in **Fig. 5** in which are shown the concentrations of products P_1 and P_2 against the rate of heating. Under classical heating (slow heating) a mixture of P_1 and P_2 is obtained. By modifying the heating rate it is possible to obtain P_1 as the principal product.

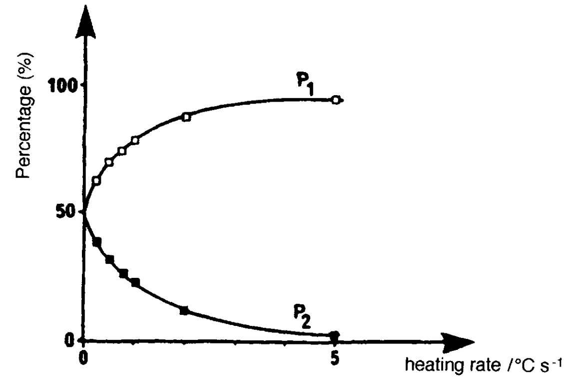


Fig. 5 Percentage of P_1 and P_2 *vs* heating rate (Reproduced with permission from ref. 25, D. Stuerga, K. Gonon and M. Lallemant, *Tetrahedron*, 1993, **49**, 6229; copyright Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, UK OX5 1GB)

The second situation, which is shown in **Fig. 6**, is described as inversion. Under classical conditions essentially only P_2 is obtained, while with microwaves, or very rapid heating, P_1 is basically the only product. This situation is very interesting since changes in reactivity induced by heating rate may be envisaged.

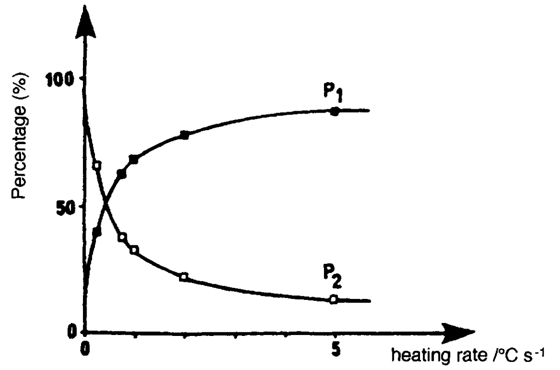


Fig. 6 Percentage of P_1 and P_2 *vs* heating rate (Reproduced with permission from ref. 25, D. Stuerga, K. Gonon and M. Lallemant, *Tetrahedron*, 1993, **49**, 6229; copyright Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, UK OX5 1GB)

The authors have demonstrated that the induced selectivity in the sulfonation of naphthalene leading to either naphthalene-1- and -2-sulfonic acids (1- and 2-NSA) is a function of the applied power (**Fig. 7**).

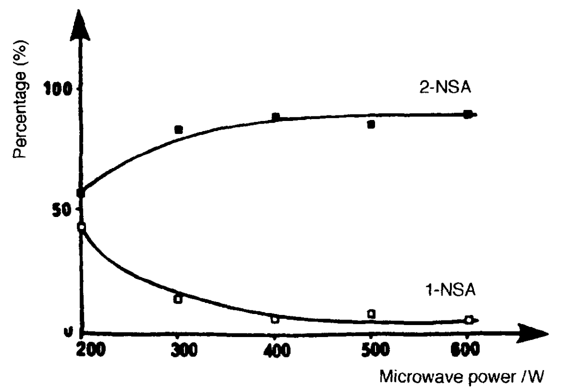
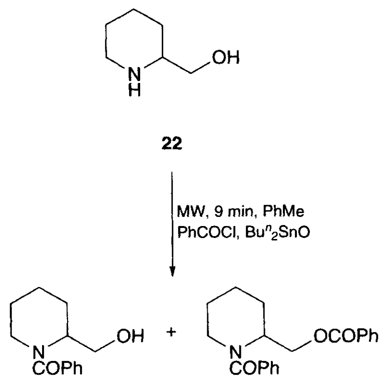


Fig. 7 Percentage of 1- and 2-NSA *vs* microwave power (Reproduced with permission from D. Stuerga, K. Gonon and M. Lallemant, *Tetrahedron*, 1993, **49**, 6229; copyright Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, UK OX5 1GB)



A **B**

Power (W)	Yield of **A** (%)	Yield of **B** (%)
445	93	5
815	78	14

Scheme 21

This possibility opens up new ways of accessing kinetically controlled products, and shows that in the presence or absence of a specific effect, microwave heating has, in addition to its ability to reduce reaction times, other important applications in the control of chemo-, regio- and stereo-selectivity.

Several authors have found differences in selectivity in other reactions carried out with microwaves when compared to classical heating. Following the nomenclature used by Stuerga *et al.*,[25] we will classify these as examples of induced selectivity and inversion of selectivity.

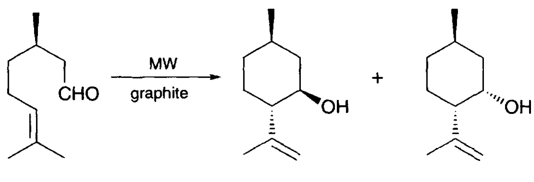
5.1 Induced selectivity

Apart from the case of sulfonation of naphthalene, other cases of induced selectivity can be found in the literature, as for example, in the acylation of polyols[45] and amino alcohols **22** (**Scheme 21**)[46] catalysed by dibutyltin oxide. The chemoselectivity of this reaction depends on the power applied during irradiation.

The stereoselectivity obtained in the cyclisation of (+)-citronellal **23** to (−)-isopulegol **24** and (+)-neoisopulegol **25** on graphite can be altered under microwave irradiation (**Scheme 22**).[47] (−)-Isopulegol is always the principal diastereoisomer regardless of the method of heating, but using microwaves the amount of (+) neoisopulegol increases to 30%.

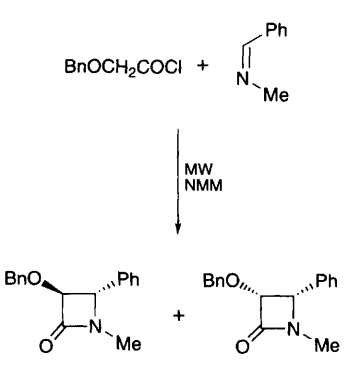
Bose *et al.*[48] have found that the steric course of β-lactam formation can be influenced by controlling the irradiation power (**Scheme 23**). Thus, at low power mainly the *cis*-isomer **27** was obtained (84%; only product at 0 °C) while at high power the principal product was the *trans*-isomer **26** (55%). The failure of the *cis*-isomer to isomerise to the *trans*-compound on heating reveals a new case of induced selectivity.

The use of tetrachlorophthaloyl glycine chloride as starting material allows stereoselectivity under microwaves or normal/thermal conditions to be differentiated.[49] Thus, with microwaves the *trans*-isomer **28** is obtained exclusively, while under normal heating, mixtures containing variable



23 **24** (70%) **25** (30%)

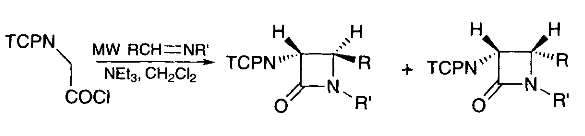
Scheme 22



26 **27**

NMM = *N*-methylmorpholine

Scheme 23



TCPN = tetrachlorophthalimido **28** **29**

Scheme 24

amounts of the *cis*-isomer **29** and *trans*-isomer **28** are obtained. (**Scheme 24, Table 2**)

Alvarez-Builla *et al.*[50] showed that the addition of 2-aminothiophenol **30** to glycidic esters under microwave irradiation (**Scheme 25**) is highly stereoselective. The *cis*:*trans* ratio in the product **31** can be modified by varying the solvent polarity. Apolar aprotic solvents favour the *cis*-isomer while protic solvents favour the *trans*-isomer. However, in apolar solvents, a gradual increase in irradiation power leads to an increase in the proportion of *trans*-isomer.

Guibé-Jampel and Loupy[51] have shown that the resolution of racemic 1-phenylethanol catalysed by supported enzymes can be enhanced under microwave irradiation (**Scheme 26**). The authors suggest that the specificity of the reaction can be attributed to an improvement in the reversibility of the reaction due to better elimination of water and/or a reduction in the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$.

5.2 Inversion of selectivity

The so-called inversion of selectivity has been shown in several types or reactions. Thus, the degradation of ethyl indole-2-carboxylate **32** with 0.2 M NaOH described by Strauss *et al.*[3] can lead to the formation of indole if the power input allows a temperature of 255 °C to be attained, or to indole-2-carboxylic acid if the temperature is limited to 200 °C (**Scheme 27**). Moreover, in this report the importance of temperature control by way of a specially designed oven was demonstrated.

In the alkylation of 1,2,4-triazole[52] with benzyl chloride, the use of microwaves allows the pure *N*-1 alkylated product **33** to be obtained, while with the classical route quaternisation occurs exclusively (**Scheme 28**).

Herradón[53] has carried out a study on the selective benzoylation of polyols by microwave irradiation in which excellent results were achieved. In the example shown, **34**→**35** the reaction carried out under radiation and in the presence of dibutyltin oxide leads exclusively to the product benzoylated in the C-2 position, which forms by way of a dibutyltin acetal catalysing and controlling the direction of the reaction (**Scheme 29**). Under classical conditions, the non-catalysed acylation is equally as fast as the tin catalysed reaction; hence there is no advantage in using the tin species.

Ley and Mynett[54] carried out the deprotection of pivalic esters **36** on alumina with microwave activation in the absence of solvent, and it was shown that selective deprotection of the 6-position could be performed without migration of groups or isomerisation of the anomeric centre (**Scheme 30**). Yields of the order of 90% of **37** were obtained, which are not possible by means of normal heating.

Similarly, Varma *et al.*[55] have studied the selective deprotection of certain diacetates **38** in the absence of solvent, in which mono- or di-deprotection was controlled by the reaction time as outlined in **Scheme 31**; mono-deprotection was not possible under conventional heating.

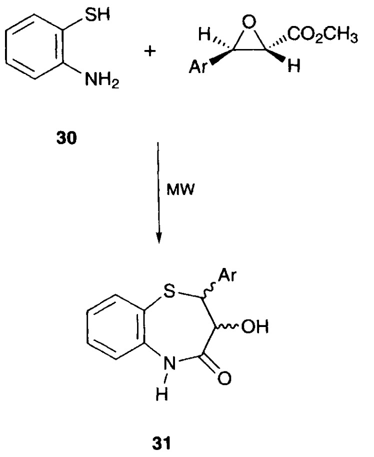
There are also several examples of inversion of regioselectivity to be found in heterocyclic chemistry. Thus Claramunt *et al.*[56,57] have reported that while the reaction of 1-bromoadamantane **39** with pyrazole in an autoclave at 230 °C yields exclusively 4-(1-adamantyl)pyrazole **40**, when carried out in a microwave oven the reactions leads to the almost pure corresponding 3-substituted isomer **41** (44%) (**Scheme 32**).

The reaction of 2-pyridone with benzyl halides in the absence of solvent,[58] normally gives *N*-alkylation, *i.e.* **45**, while microwave irradiation leads to C-alkylation *i.e.* **42–44**. With microwaves the selectivity may be controlled by the irradiation power and the nature of leaving group. The previously mentioned phenomenon of induced selectivity can be observed, since at low power alkylation occurs mainly at C-5, while at higher irradiation power a slight excess of the C-3 product is obtained. Moreover, in the case of benzyl bromide,

Table 2 Synthesis of *β*-lactams **28** and **29**

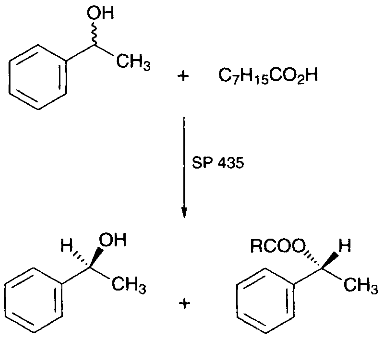
R	R′	Yield (%)[a]	**28**:**29**	
			Microwaves	Classical heating
Ph	PMP[b]	83 (57)	100:0	55:45
PMP	PMP	89 (52)	100:0	10:90
Styryl	PMP	99 (77)	0:100	0:100
Furyl	PMP	90 (53)	100:0	20:80
Ph	Bn	83	80:20	

[a] The yields in brackets refer to isolated *β*-lactams obtained by classical heating (CH)
[b] PMP = *p*-methoxyphenyl



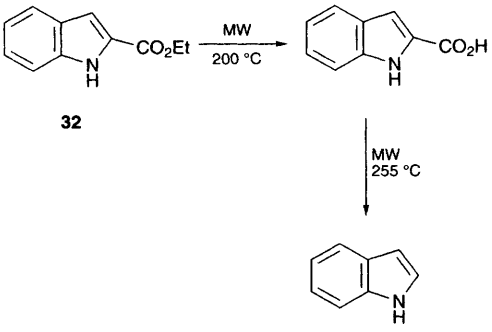
PhMe, 390 W, 20 min, (75 %, *cis*:*trans* 9: 1)
AcOH, 490 W, 10 min, (84 %, *cis*:*trans* 1: 9)

Scheme 25

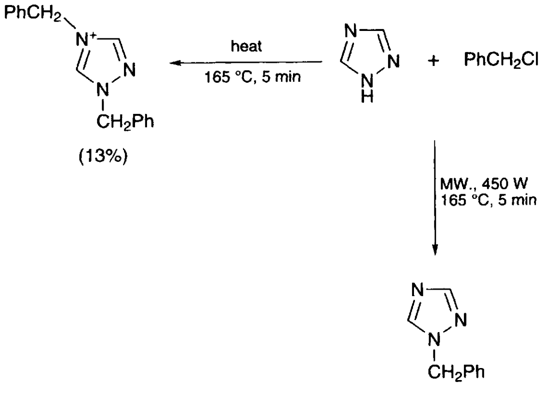


Method of heating	Time (min)	Temp (°C)	Yield (%)	ee alcohol (*S*) (%)
Classical heating	10	78	48	62
Microwaves (300 + 80 W)	1 + 4	95	47	86
Microwaves (60 + 20 W)	5 + 5	78	52	93

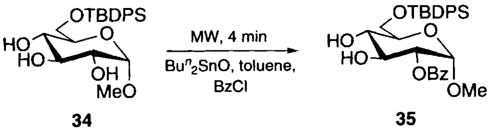
Scheme 26



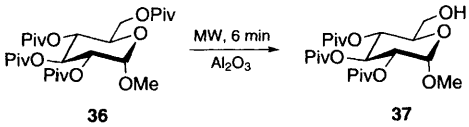
Scheme 27



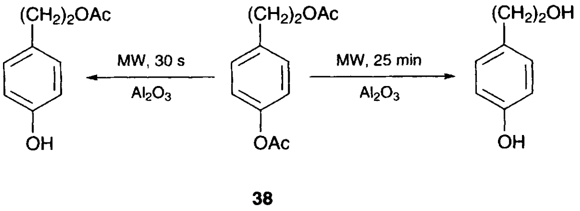
Scheme 28



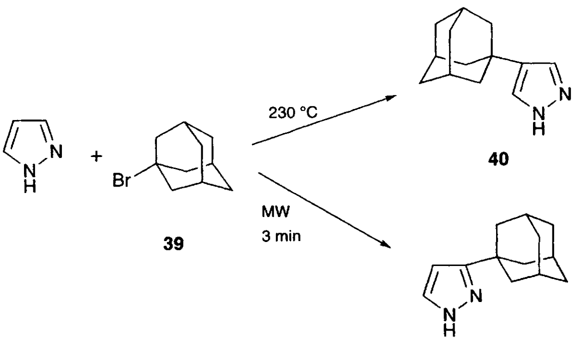
Scheme 29



Scheme 30

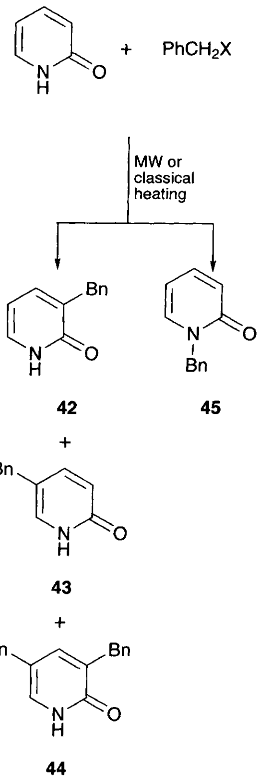


Scheme 31



Scheme 32

C-alkylation is observed, while with benzyl chloride *N*-alkylation results (**Scheme 33, Table 3**) .

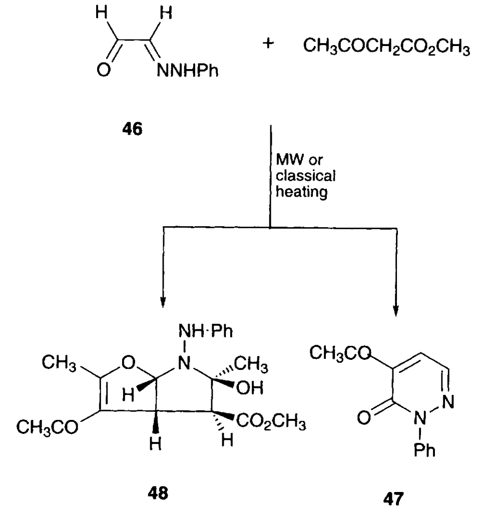


Scheme 33

Table 3 Benzylation of 2-pyridone: product distribution

X	Conditions	*t*/min	*T*/°C	Product N:C
Cl	Microwaves, 780 W	5	178	100:0
	Classical heating	5	178	100:0
Br	Microwaves, 450 W	5	196	0:100
	Microwaves, 150 W	5	81	100:0
	Classical heating	5	196	100:0
I	Microwaves, 450 W	2.5	180	0:100
	Microwaves, 150 W	10	160	0:100
	Classical heating	5	160	100:0

In the reaction of the glyoxal monohydrazone **46** with methyl acetoacetate in the absence of solvent, Hamelin *et al.*[59] have reported that pyridazinone **47** and the heterobicyclo compound **48** are formed in a ratio of 7:93 under normal heating. Employing microwaves however leads to an inversion in reactivity resulting in a product ratio of 85:15 (**Scheme 34**).



Scheme 34

6 Conclusions

The results compiled in this review show that microwave irradiation is more than just a method for performing reactions in a shorter time period. It has been demonstrated that numerous processes can not only be improved upon, but can be controlled in the case of competitive reactions, or with respect to chemo-, regio- or stereo-selectivity may be modified or inverted.

The most interesting and spectacular results, however, are still to come. In order that they can be realised, the design of new equipment is necessary in which there is proper control of power and reaction temperature and where losses in the waveguide are minimised; in other words, instruments that provide for better exploitation of the radiation.

Furthermore, the design of more reliable instruments should provide for a more complete understanding of the theoretical basis of the technique which would make it possible to know '*a priori*' which reactions could be improved upon and which changes in selectivity should be expected on employing microwaves.

From an organic synthesis point of view, further examples will assist in the understanding of the effects caused by microwave irradiation. Moreover, it is of paramount importance to test new reactions that fail to occur, or which take place with some difficulty, by means of classical heating. Finally, it is desirable to introduce the concept of microwave irradiation and its synthetic applications in chemical education so that newly trained chemists become accustomed to this means of performing reactions and the concept of heating that is different from the usual.

The success of microwave technology is now manifest in the development of the first industrial applications.[60] For example, Dow Elanco have installed a microwave chlorination plant and researchers from DuPont have announced the development of a method for the microwave preparation of hydrogen cyanide on a laboratory scale which avoids the need to transport this material.

7 Acknowledgements

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