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A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations

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Microwave (MW) activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry. The number of annual publications on microwave assisted organic chemistry is growing rapidly with almost one thousand publications in print since the pioneering work of Gedye¹ in 1986 (Fig. 1).

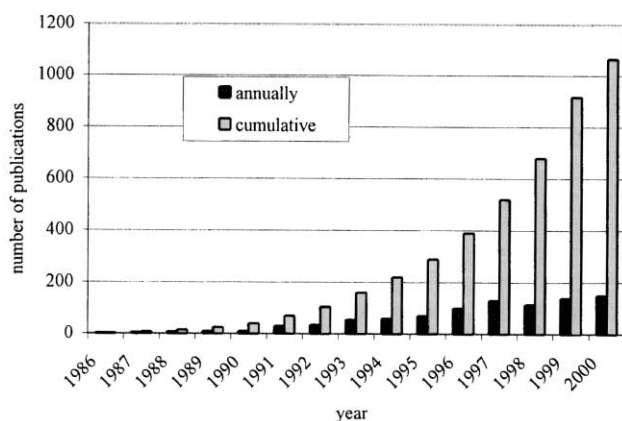


Figure 1. Number of publications dealing with microwave irradiation in organic synthesis for the period 1986–2000.

Most of these publications describe important accelerations for a wide range of organic reactions especially when carried out under solvent-free conditions. The combination of solvent-free reactions conditions and microwave irradiation leads to large reductions in reaction times, enhancements in conversions and, sometimes,^{2,3} in selectivity with several advantages of the eco-friendly approach, termed green chemistry.

A considerable number of these reports are however based on inaccurate or non-founded comparisons with classical conditions which do not allow unequivocal conclusions to

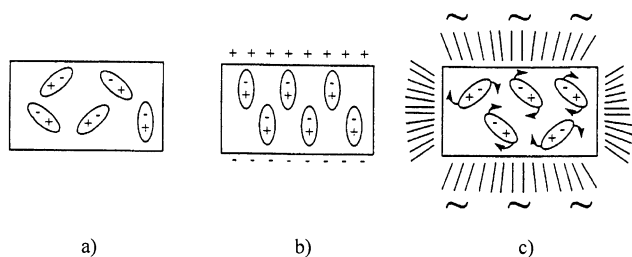
be made concerning microwave effects. For this reason, some apparent contradictions and controversies have appeared in the literature.^{4–7} In order to try to rationalize all of the results, it is necessary to propose a plausible interpretation of the effects based on accurate and reliable data resulting from strict comparisons between reactions carried out but under otherwise microwave irradiation or conventional heating under similar conditions (reaction medium, temperature, time, pressure).^{2,8,9} A monomode microwave reactor should preferably be used which gives wave focusing (reliable homogeneity in the electric field) and accurate control of the temperature (using an optical fibre or by infrared detection) throughout the reaction.^{2,9} This gives the possibility of operating with rather similar profiles of temperature increases in both kinds of activation. Based on such strict comparisons, it then becomes possible to make an educated judgment about the suitability, or otherwise, of using microwave irradiation according to the reaction types and experimental conditions.

1. Origin of microwave effects

The acceleration of reactions by microwave exposure results from material-wave interactions leading to thermal effects (which may be easily estimated by temperature measurements) and specific (non-purely thermal) effects. Clearly, a combination of these two contributions can be responsible for the observed effects.

Thermal effects (dielectric heating) can result from dipolar polarization as a consequence of dipole–dipole interactions between polar molecules and the electromagnetic field. They originate in dissipation of energy into heat as an outcome of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at

each alternation of the electric field at a very high frequency ($\nu=2450$ MHz)^{10,11} (Scheme 1).



Scheme 1. Effects of the surrounding electric field on the mutual orientation of dipoles: (a) without any constraint, (b) submitted to a continuous electric field, (c) submitted to an alternating electric field with a high frequency.

This energy dissipation in the core of materials allows a much more regular repartition in temperature when compared to classical heating. Classical thermal phenomena (conduction, convection, radiation, etc.) only play a secondary role in the a posteriori equilibration of temperature.

In this range of frequency, the charge space polarization¹² can also intervene and can be of prime importance with semiconductors since it concerns materials which contain free conduction electrons. This phenomenon is essential in heating solid particles, more or less magnetic, such as a variety of mineral oxides or metallic species (Table 1).

Table 1. Some significant thermal effects of molecules when submitted to microwave exposure (domestic oven, 600 W)

Liquid ^{13,14}	Temperature after 1 min irradiation (°C)	Boiling point (°C)	Dipolar moment (Debye)
H ₂ O	81	100	5.9
EtOH	78	78	5.8
<i>n</i> -C ₃ H ₇ OH	106	137	5.7
CH ₃ CO ₂ H	110	119	5.6
DMF	131	153	10.8
<i>n</i> -C ₆ H ₁₄	25	98	0.0
CCl ₄	28	77	0.0

Solid species ¹⁵	Irradiation time (min)	Final temperature (°C)
Al	6	577
C	1	1283
Co	3	697
Cu	7	228
Fe	7	768
Zn	3	581
CuO	6	67
Cu ₂ O	6	1012
Fe ₃ O ₄	3	1258
MnO	6	113
MnO ₂	6	1287
WO ₃	6	581
ZnO	5	1270

For liquid products (solvents), only polar molecules selectively absorb microwaves, non-polar molecules being inert to microwave dielectric loss. In this context of efficient microwave absorption, it has also been shown that higher boiling point values could be observed when solvents are submitted to microwave irradiation conditions when compared with conventional heating. This effect, called

the ‘superheating effect’^{16,17} has been attributed to some retardation of nucleation in microwave heating (Table 2).

Table 2. Boiling points of some typical polar solvents (°C)

Solvent	Normal conditions	MW exposure	Difference
Water	100	105	5
1-Butanol	117	138	21
2-Butanol	98	127	29
Methanol	65	84	19
1-Pentanol	136	157	21
1-Heptanol	176	208	32
Acetone	56	89	33
Ethyl acetate	77	102	25
Tetrahydrofuran	67	103	36
Acetonitrile	82	120	38

This superheating effect can often be observed using domestic multimode systems in the absence of any stirring. In Table 3, the results of measurements in a monomode system in the absence or presence of a nucleation regulator (boiling chips) are collected.

Typical profiles of temperatures increase and boiling point measurements using a monomode system are shown in Fig. 2.

The superheating effect is therefore clearly related to the

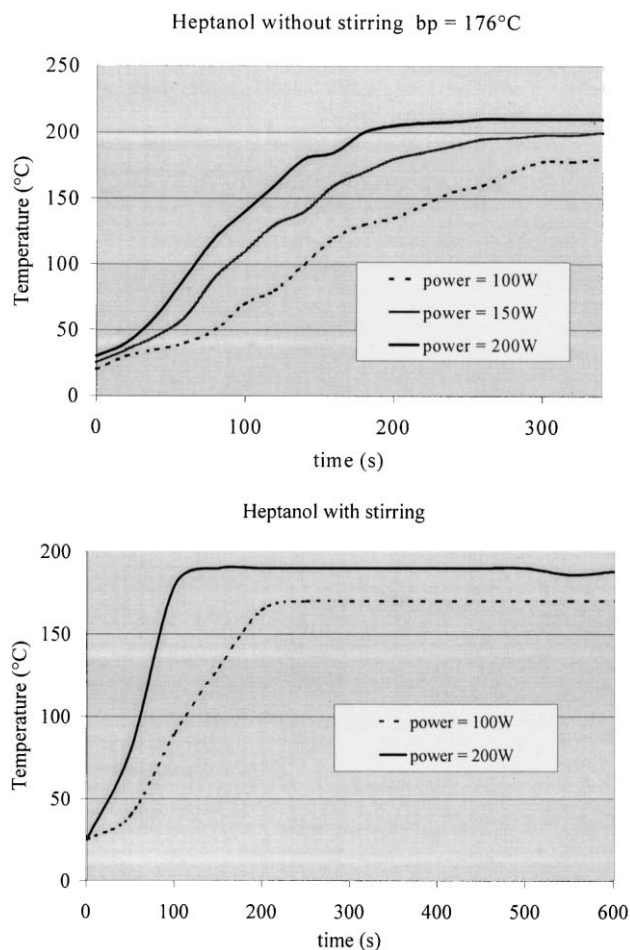


Figure 2. Profiles of temperature increase of heptanol when submitted to MW irradiation.

Table 3. Boiling points of some polar solvents under MW irradiation in the absence or presence of a nucleation regulator (°C)

Solvent	Boiling point	Microwave exposure		
		Multimode ^{16,17}	Monomode (100 W)	Monomode+boiling chips
Water	100	105	100	100
1-Heptanol	176	208	180	173
Ethyl acetate	77	102	92	77
Chloroform	61	89	85	62
Cyclohexanone	155	186	168	155

effect of stirring and the presence of a nucleation regulator.¹⁸ It is also related to the microwave power. This effect is expected to disappear if the experiments are carried out with well-stirred mixtures¹⁹ using low microwave power. It could prevail in the absence of stirring, i.e. in closed vessels inside a domestic microwave oven.

2. Specific microwave effects

The origin of specific microwave effects is two-fold, namely those which are not purely thermal (vide infra (i) and (ii)) and a thermal effect (iii) connected to the intervention of 'hot spots'. Non-purely thermal effects (other than simple dielectric heating) can be envisaged to have multiple origins. These effects can be rationalized by consideration under the Arrhenius law^{20,21} [$k = A \exp(-\Delta G^\ddagger/RT)$] and can result from modifications in each of the terms in this equation.

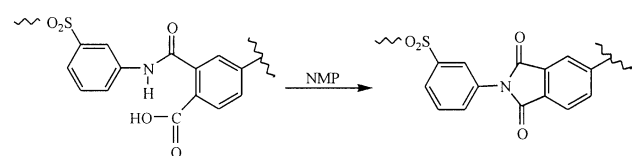
(i) Thus, the increase in the pre-exponential factor A which is representative of the probability of molecular impacts. The collision efficiency can be effectively influenced by mutual orientation of polar molecules involved in the reaction. As this factor is dependent on the vibration frequency of the atoms at the reaction interface, it could be postulated that the microwave field might affect this. Binner et al.²² explained the increased reaction rates observed during the microwave synthesis of titanium carbide in this way:



Calculations have shown that the faster diffusion rates might be explained by an increase in the factor A with no change in activation energy.

(ii) Decrease in activation energy ΔG^\ddagger is certainly a main effect. When considering the contribution of enthalpy and entropy to the value of ΔG^\ddagger [$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$], it may be predicted that the magnitude of the $-T\Delta S^\ddagger$ term would increase in a microwave-induced reaction this being more organized when compared to classical heating as a consequence of dipolar polarization. Lewis et al.²³ presented experimental evidence for such an assumption after measurements of rate constants according to temperature for the unimolecular imidization of a polyamic acid (Eq. (1), Fig. 3, Table 4).

The apparent activation energy is evidently largely reduced. The same explanation, i.e. a decrease in ΔG^\ddagger was also proposed for the decomposition reaction of sodium hydrogen carbonate in aqueous solution.²⁴



NMP = N-methylpyrrolidinone

(1)

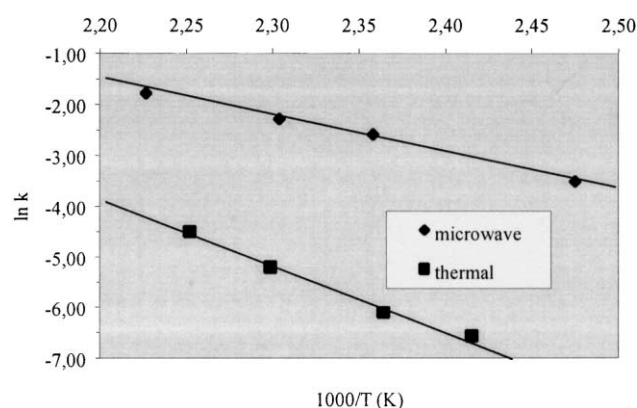


Figure 3. First order kinetic plots for microwave (MW) and thermal (Δ) activation for the imidization reaction.

Table 4. Results from the Arrhenius plots in Fig. 3

Activation mode	ΔH^\ddagger (kJ/mol)	log A
MW	57±5	13±1
Δ	105±14	24±4

(iii) Intervention of localized microscopic high temperatures^{8,23,25} as advocated in sonochemistry to justify the sonochemical effect. It was suggested^{5,20} that, in some examples, MW activation could originate from hot spots generated by dielectric relaxation on a molecular scale.

3. Medium effects

Microwave effects should additionally be considered according to the reaction medium. Solvent effects are of particular importance.^{26,27}

(i) If polar solvents are concerned, either protic (e.g. alcohols) or aprotic (e.g. DMF, CH_3CN , DMSO etc.), the main interaction may occur between MW and polar molecules of the solvent. Energy transfer is from the solvent molecules

(in a large excess) to the reaction mixtures and the reactants, and it would be expected that any specific MW effects on the reactants would be masked by solvent absorption of the field. The reaction rates should therefore be nearly the same as those under conventional heating (Δ).

This is essentially true as evidenced by the rates of esterification in alcoholic media of propan-1-ol with ethanoic acid (Fig. 4)²⁸ or of propan-2-ol with mesitoic acid.²⁹

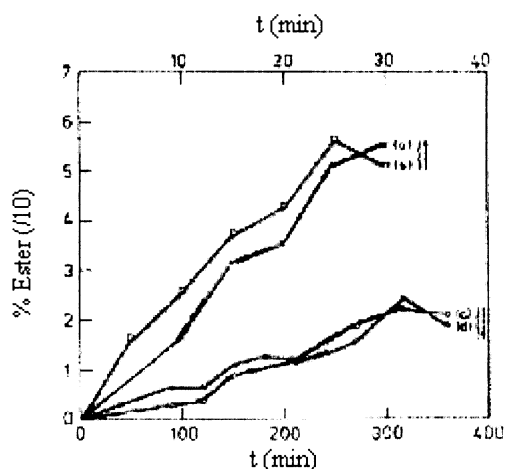
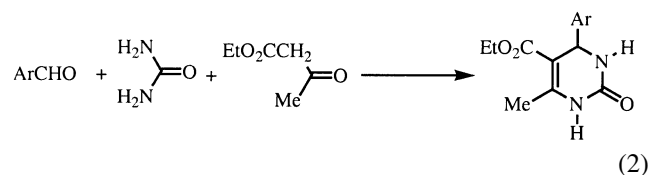


Figure 4. Concentration of ester according to time. Catalyst: H_2SO_4 (a) Δ (b) MW; Silica (c) Δ (d) MW.

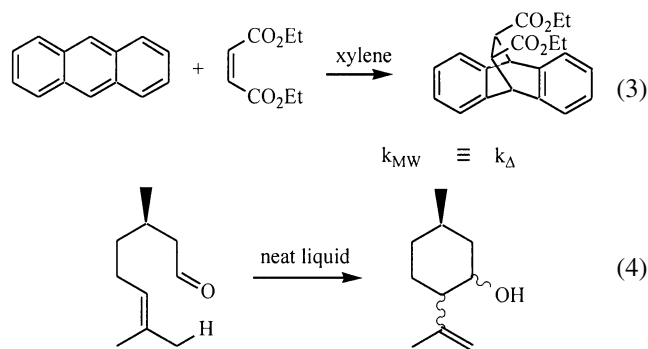
More recently,³⁰ the microwave-mediated Biginelli dihydropyrimidine synthesis (Eq. (2)) was reinvestigated using a purpose-built commercial microwave reactor with on-line temperature, pressure and microwave power control. Transformations carried out under microwave heating at atmospheric pressure in ethanol solution showed neither a rate increase nor an increase in yield when the temperature was identical to that used for conventional thermal heating. The only significant rate and yield enhancements were found when the reaction was performed under solvent-free conditions in an open system.



The absence of a specific MW effect also became apparent from several experiments carefully conducted in alcohols or in DMF.⁶ As described above, however some rather small differences could appear, taking into account the superheating effect of the solvent under MW. This probably occurs in the isomerization of safrole and eugenol in refluxing ethanol³¹ (MW 1 h, Δ 5 h to obtain equivalent yields).

(ii) More interesting is the use of non-polar solvents (e.g. xylene, toluene, carbon tetrachloride, hydrocarbons) as they are transparent to MW and only weakly absorb microwaves. They can therefore allow specific absorption by the reac-

tants. If these reactants are polar, energy transfer occurs from the reactants to the solvent and the results may be different under MW and Δ . This effect seems to be clearly dependent on the reaction and is therefore the subject of controversy. In refluxing xylene, for example, no MW-specific effects were observed for Diels–Alder⁴ (Eq. (3)) or ene reactions⁵ (Eq. (4)), whereas important specific effects were described for aryldiazepinone synthesis,^{32a,b} although some doubts on the results were subsequently reported.³³



These examples will be discussed and explained later on the dependence of MW effects on the reaction mechanisms.

Clearly, solvent influence seems to be of great importance with regard to the possibility of MW-specific effects. These could decrease when the polarity of the solvent is increased. This influence was shown in at least two studies from Berlan et al.²⁰ and, more recently, from Bogdal.³⁴ In the first study, a non-symmetrical Diels–Alder reaction acceleration under MW was much more apparent in xylene when compared to the more polar dibutyl ether (Fig. 5).

In the second investigation,³⁴ involving a coumarin synthesis by Knoevenagel condensation, supported by rate constant measurements and activation energy calculations, it was found that MW influence was important when the reaction was carried out in toluene whereas it was noticeably reduced in ethanol.

(iii) Microwave effects are mostly likely to be observed in solvent-free reactions.² In addition to the preparative interest of these methods in terms of use, separation, and economical, safe and clean procedures, absorption of microwave radiation should now be limited only to the reactive species. The possible specific effects will therefore be optimal since they are not moderated or impeded by solvents. They can be accomplished according to three following methods:^{2,35}

(a) reactions between the neat reagents in quasi-equivalent amounts, requiring preferably at least one liquid phase in heterogeneous media and leading to interfacial reactions,³⁶

(b) solid–liquid phase transfer catalysis (PTC) conditions, in the case of anionic reactions using the liquid electrophile as both reactant and organic phase and a catalytic amount of tetraalkylammonium salts as the transfer agent³⁷ and

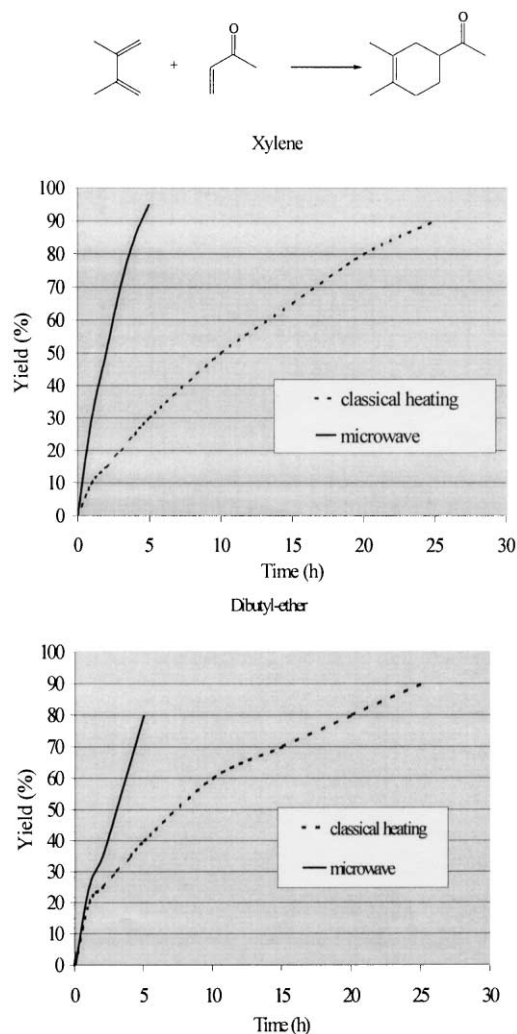
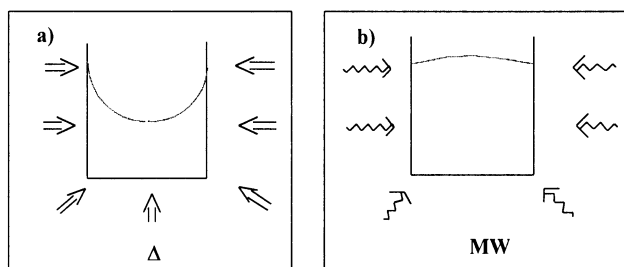


Figure 5. Yields against time for the reaction at 95°C.

(c) reactions using impregnated reagents on solid mineral supports (aluminas, silicas, clays) in dry media.^{2,3,38}

These procedures coupled with microwave activation have proven beneficial and have led to a lot of success stories which are described in several reviews.^{2,3,38–41}

Some apparent specific effects could however arise from the supports. The mineral supports are generally poor heat conductors, i.e. significant gradients in temperature can be developed inside the vessels under conventional heating, whereas they behave as efficient absorbers of microwave



Scheme 2. Gradients in temperature for materials submitted either to traditional heating (a), or to microwave radiation (b).

energy with consequently more homogeneity in temperature (Scheme 2).

4. Effects according to reaction mechanisms

Microwave effects result from material-wave interactions and, due to the dipolar polarization phenomenon, the greater the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature¹³ is considered. In terms of reactivity and kinetics, the specific effect has therefore to be considered according to the reaction mechanism and particularly with regard to how the polarity of the system is altered during the progress of the reaction.

Specific microwave effects can be expected for the polar mechanism, when the polarity is increased during the reaction from the ground state towards the transition state (as more or less implied by Abramovich in the conclusion of his review in 1991⁴⁰). The outcome is essentially dependent on the medium and the reaction mechanism. If stabilization of the transition state (TS) is more effective than that of the ground state (GS), this results in an enhancement of reactivity by a decrease in the activation energy (Fig. 6).

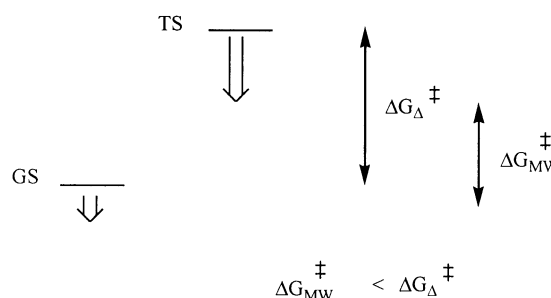


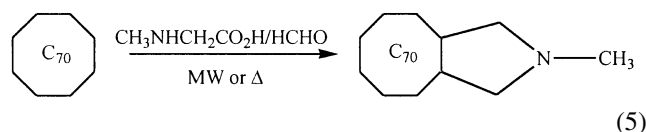
Figure 6. Relative stabilization of a more polar TS when compared to the GS (polar mechanism).

4.1. Isopolar transition state reactions

Isopolar activated complexes differ very little or not at all in charge separation or charge distribution from the corresponding initial reactants. These complexes are formed with pericyclic reactions such as Diels–Alder cycloadditions, Cope rearrangement or ene reactions. Ground and transition states present a priori identical polarities as no charges are developed during the reaction path. Following this rule, no specific microwave effects would be expected on these reactions, as has been verified when the reactions were performed in a non-polar solvent.^{4,5} The reactions also exhibit small or negligible solvent effects for the same reasons.⁴²

Nevertheless, such a conclusion is connected to the synchronous character of the mechanism. If a stepwise process is involved (non-simultaneous formation of the two new bonds), as is the situation when dienes and (or) dienophiles are unsymmetrical or in hetero Diels–Alder reactions, a specific microwave effect could intervene as charges are developed in the transition state. This could certainly be

the case for several cycloadditions^{43,44} and particularly for 1,3-dipolar cycloadditions.⁴⁵ Such an assumption was verified when considering theoretical calculations predicting an asynchronous mechanism in the cycloaddition of *N*-methylazomethine ylide to C₇₀ fullerene²⁶ (Eq. (5)).



During the course of a study of the cycloaddition of azido-methyl-diethylphosphonate with acetylenes and enamines leading to alkyltriazoles under solvent-free conditions, we have observed that specific effects may be involved as a function of the nature of the substituents on the dipolarophiles⁴⁶ (Eq. (6), Table 5).

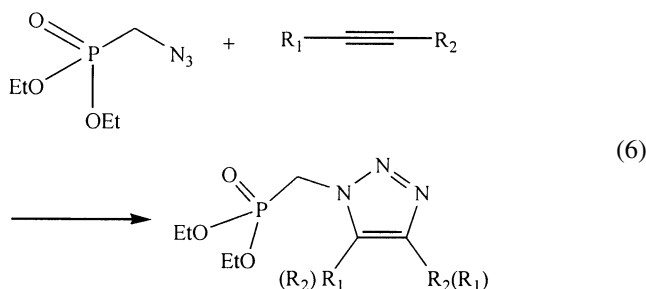


Table 5. Thermal or microwave activation for the cycloaddition depicted in Eq. (6)

R ₁	R ₂	Activation	Conditions		
			t (min)	T (°C)	Yields (%) ^a
CH ₃	P(O)(OEt) ₂	Δ	20	90	5
		MW	20	90	78
H	CO ₂ Et	Δ	5	100	70
		MW	5	100	92
C ₆ H ₅	CO ₂ Et	Δ	10	160	>98
		MW	10	160	>98
H	C ₆ H ₅	Δ	30	120	40
		MW	30	120	>98
H	CH ₂ OH	Δ	30	100	40
		MW	30	100	>98

^a The ratio of the two isomers formed remained identical under both conditions of activation.

The synthesis of biologically significant fluorinated heterocyclic compounds was accomplished via the 1,3-dipolar cycloaddition of nitrones to fluorinated dipolarophiles.⁴⁷ This reaction was noticeably improved under solvent-free conditions and using microwave irradiation (Eq. (7), Table 6).

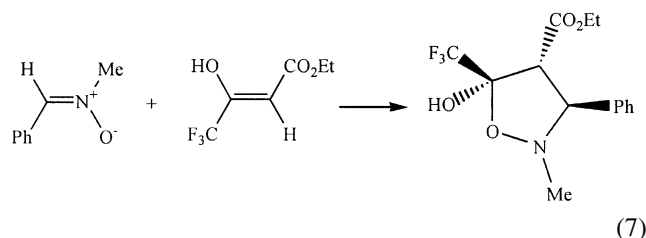


Table 6. Thermal or microwave activation for the cycloaddition depicted in Eq. (7)

Activation	Conditions			Yield (%)
	Solvent	Time	Temperature (°C)	
Δ	Toluene	24 h	110	65
MW	None	3 min	119	98
Δ	None	3 min	119	64
Δ	None	30 min	119	98

It can be seen that there is a definite advantage in operating under solvent-free conditions. A microwave effect is evident since after 3 min as the yield increases from 64 to 98%. Prolongation of the reaction time under classical heating led to an equivalent result. The microwave effect is rather limited here due to a near-synchronous mechanism.

4.2. Bimolecular reactions between neutral reactants leading to charged products

Typical reactions are amine or phosphine alkylation or addition to a carbonyl group (Scheme 3). In these examples, due to development of dipoles in the TS, we are concerned with an increase of polarity during the course of the reaction starting from the GS towards the TS. Favourable microwave effects are consequently expected.

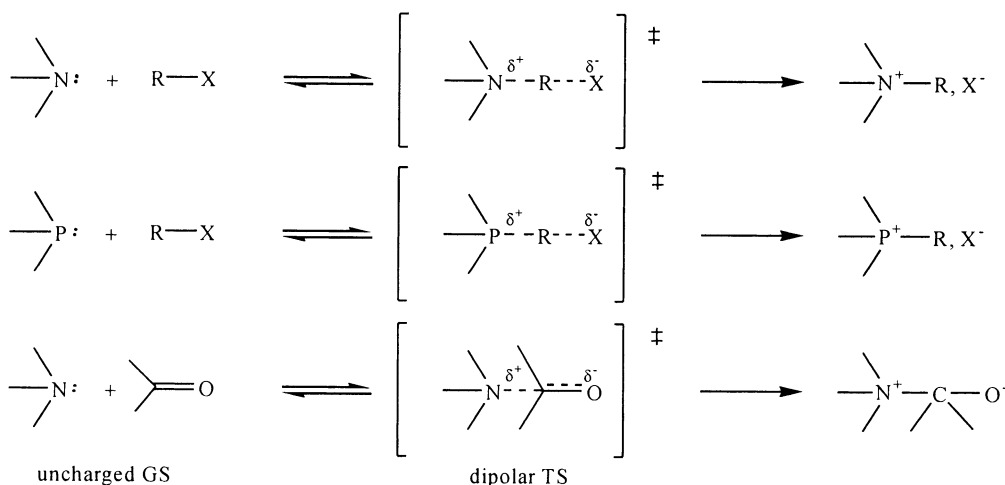
The magnitude of these effects may be related to the nature of substituents α to N or P and to the leaving group structure as exemplified by several observations that will be described and discussed later.

4.3. Anionic bimolecular reactions involving neutral electrophiles

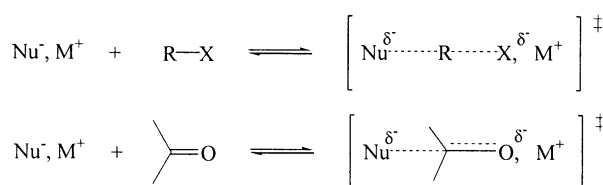
These reactions comprise nucleophilic S_N2 substitutions, β-eliminations and nucleophilic additions to carbonyl compounds or activated double bonds, etc. They involve the reactivity of anionic species Nu⁻ associated as ion-pairs having several possible structures with counterions M⁺⁴⁸ (Scheme 4).

The transition states are composed of loose ion pairs in so far as they involve a charge delocalized anion, thereby conferring an enhancement in polarity with respect to the ground states (in which the ion pairs are tighter) due to an increase in anionic dissociation as the more bulky product anion is formed. As a consequence, specific microwave effects, directly connected to polarity enhancement, should depend on the structure of reactive ion pairs in the GS if:

- tight ion pairs (between two hard ions) are involved in the reaction, the microwave accelerating effect then becoming more important, due to enhancement in ionic dissociation during the course of the reaction as tight ion pairs (GS) are transformed into more polar loose ion pairs (TS), and
- on the other hand, loose ion pairs (between soft ions) are involved, the microwave acceleration here being limited as ionic interactions are only slightly modified from GS to TS.



Scheme 3. R=Alkyl group, X=halide.

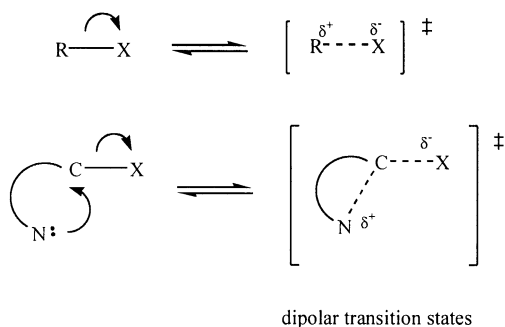


Scheme 4.

This duality in behaviours of some S_N2 reactions can be foreseen and observed (vide infra) by comparing reactions involving hard or soft nucleophilic anionic reagents according to the cation and the leaving group.

4.4. Unimolecular reactions

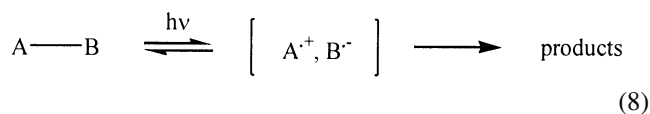
Entropic contributions towards the acceleration of first order reactions by microwaves should be negligible ($\Delta S^\ddagger = 0$). When ionisation (S_N1 or E_1) or intramolecular addition (cyclisations) processes are concerned, a microwave effect could be viewed as resulting from a polarity increase from GS to TS due to development of dipolar intermediates (Scheme 5).



Scheme 5. R=Alkyl group, X=halide.

Another interesting example in this context is the possibility of coupling between photochemical and microwave effects. Due to possible homogeneous bond breaking, the substrate

leads to dipolar intermediates constituted by ion pairs between cation and anion radicals and these are consequently prone to microwave interactions (Eq. (8)).



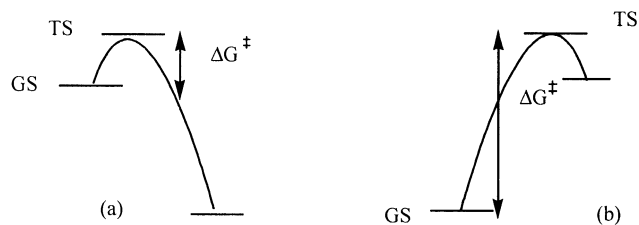
The formation and reactivity of these polar ion pairs could be at the origin of such $h\nu$ /MW coupling efficiency, as well as a microwave effect on radical pair life-times, with further practical interest lying in an electrodeless procedure.^{49–51} The microwave field generates ultraviolet irradiation in the lamp at the same time as it interacts with the studied sample, which is therefore affected by a simultaneous UV/Vis and MW irradiation.

5. Effects according to transition state position along the reaction coordinates

The position of the transition state along the reaction coordinates in relation to the well known Hammond postulate⁵² will now be considered.

If a reaction only necessitates a small activation energy, ΔG^\ddagger , the TS looks like the GS (it is depicted as a reactant-like transition state). Consequently, the polarity is only slightly modified between the GS and TS during the course of the reaction and only weak specific microwave effects can be foreseen under these conditions.

By way of contrast, a more difficult reaction implies a higher activation energy. The TS therefore occurs later along the reaction path and, consequently, the influence of polarity effects may be significantly improved. It may be assumed that a microwave effect should be more pronounced when the TS occurs later along the reaction coordinates (depicted more as a product-like transition state) and is therefore more prone to develop an increased polarity (Scheme 6).



Scheme 6. (a) Small $\Delta G^\ddagger \Rightarrow$ early TS \Rightarrow little change in polarity TS/GS \Rightarrow weak microwave effect. (b) Large $\Delta G^\ddagger \Rightarrow$ late TS \Rightarrow important change in polarity TS/GS \Rightarrow large microwave effect.

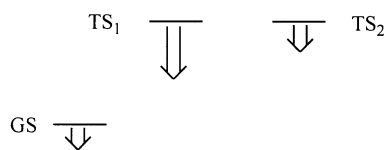
This conclusion is in agreement with a remark of Lewis who stated that “slower reacting systems tend to show a greater effect under microwave radiation than faster reacting ones”.⁵³

Consequently, a microwave effect can be important when steric effects are involved in a reaction, as exemplified by the increased magnitude of the effect for saponifications of hindered mesitoic esters relative to benzoic esters⁵⁴ (vide supra).

6. Effects on selectivities

A few examples of increased selectivities can be found in the literature^{55–60} where the steric course, and the chemo- or regioselectivity of reactions can be altered under microwave irradiation when compared to conventional heating.

As a further consequence of these assumptions, it may be foreseen that microwave effects could be important in determining the selectivity of certain reactions. When competitive reactions are involved, the GS is common for both processes. The mechanism occurring via the more polar TS could therefore be favoured under microwave radiation (Scheme 7).



Scheme 7. The more polar TS1 is more stabilized by dipole–dipole interactions with the electric field and therefore more prone to microwave effects.

Langa et al.,^{27,61,62} while conducting the cycloaddition of *N*-methylazomethine ylide with C₇₀ fullerene, proposed a rather similar approach. Theoretical calculations predict an asynchronous mechanism, suggesting that this phenomenon can be explained by considering that, under kinetic control, ‘microwave irradiation will favour the more polar path corresponding to the hardest transition state’.

7. Some illustrative examples

In order to illustrate the above trends, we now present some typical illustrative examples which have been selected because strict comparisons between microwave and classical heating activation were ascertained under similar

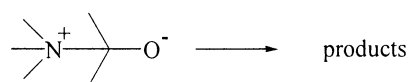
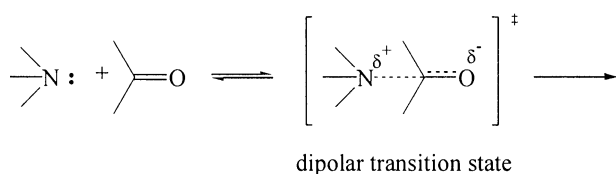
conditions (time, temperature, pressure, etc.) for the same reaction medium and using preferably a monomode system equipped with stirring. They mostly involve reactions performed under solvent-free conditions or, in some cases, in a non-polar solvent as these conditions are also favorable for the observation of microwave effects.

7.1. Bimolecular reactions between neutral reactants

These reactions are among the most propitious to reveal specific microwave effects as the polarity is evidently increased during the reaction course from a neutral ground state to a dipolar transition state.

7.1.1. Nucleophilic additions to carbonyl compounds.

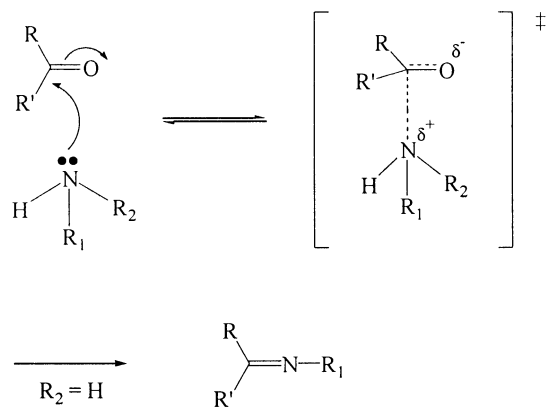
The most typical situation can be depicted for amine additions to a carbonyl group (Eq. (9))



(9)

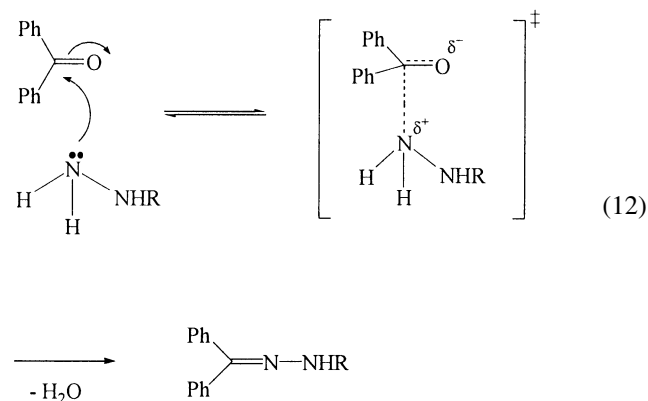
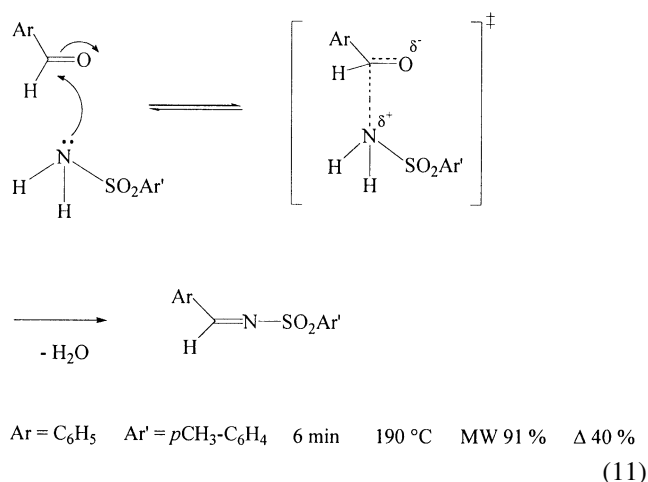
This example covers very classical processes such as the syntheses of a wide variety of compounds including imines, enamines, amides, oxazolines, hydrazones etc.

7.1.1.1. Imine or enamine synthesis. It was shown by Varma et al.⁶³ that the reactions of primary and secondary amines with aldehydes and ketones are substantially accelerated by microwaves under solvent-free conditions in the presence of montmorillonite K10 clay to afford high yields of imines and enamines (Eq. (10)).



(10)

In a similar type of reaction, the solvent-free synthesis of *N*-sulfonylimines was described with a large specific microwave effect⁶⁴ (Eq. (11)).



7.1.1.2. Hydrazone synthesis. In a typical example, a mixture of benzophenone and hydrazine hydrate in toluene gave a 95% yield of the hydrazone within 20 min⁶⁵ (Eq. (12)).

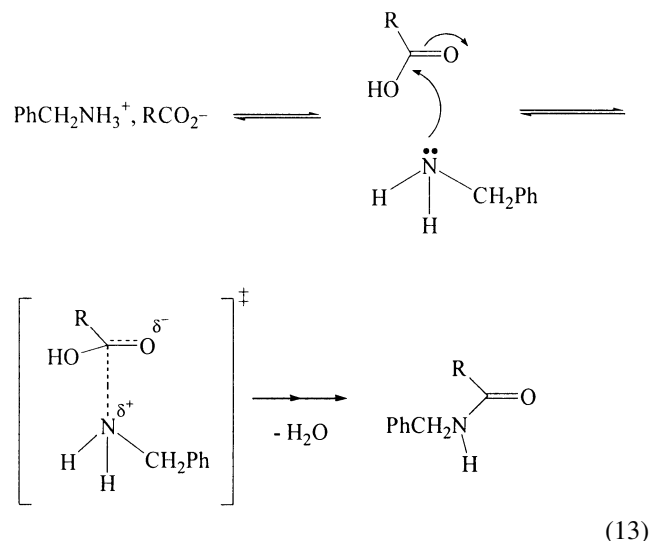
Subsequently, the hydrazone was treated with KOH under MW to undergo Wolff–Kishner reduction (leading to PhCH₂Ph) within 25–30 min in excellent yields (95%).

7.1.1.3. Amidation of carboxylic acids. Uncatalysed amidations of acids have been realized under solvent-free conditions with a very important microwave effect.⁶⁶ The best results were obtained using a slight excess of either amine or acid (1.5 equiv.).

Table 7. Reaction of benzylamine with carboxylic acids at 150°C during 30 min

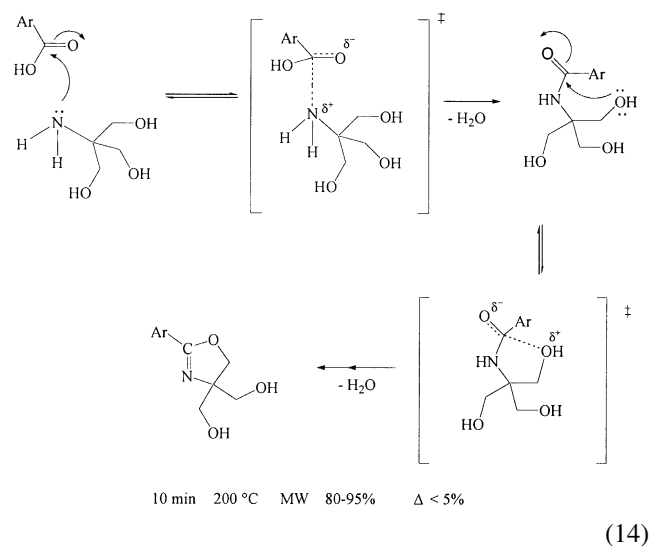
R	Amine/acid	Yield %	
		MW	Δ
Ph	1:1	10	10
	1.5:1	75	17
	1:1.5	80	8
PhCH ₂	1:1	80	63
	1.5:1	93	40
	1:1.5	92	72
CH ₃ (CH ₂) ₈	1:1	85	49

The reaction involves thermolysis of the previously formed ammonium salt (acid–base equilibrium), and is promoted by nucleophilic attack of the amine on the carbonyl moiety of the acid and removal of water at high temperature. The large difference in yields (MW ≫ Δ) may be a consequence of the polar TS interaction with the electric field (Eq. (13), Table 7).



If it is considered that, at 150°C, water can be removed equally under both types of activation, the noticeable difference in yields is clearly indicative of an improvement in the nucleophilic addition of the amine to the carbonyl group when performed under microwave irradiation with important specific effects.

7.1.1.4. Synthesis of 2-oxazolines. Oxazolines can be readily synthesized via a non-catalysed solvent-free procedure by two successive nucleophilic additions on a carbonyl group with the formation of an amide as an intermediate⁶⁷ (Eq. (14)).



7.1.1.5. Synthesis of aminotoluenesulfonamides. The title compounds were prepared by reacting aromatic aldehydes with sulfonamides under microwave in the

presence of a few drops of DMF to allow better energy transfer⁶⁸ (Eq. (15), Table 8).

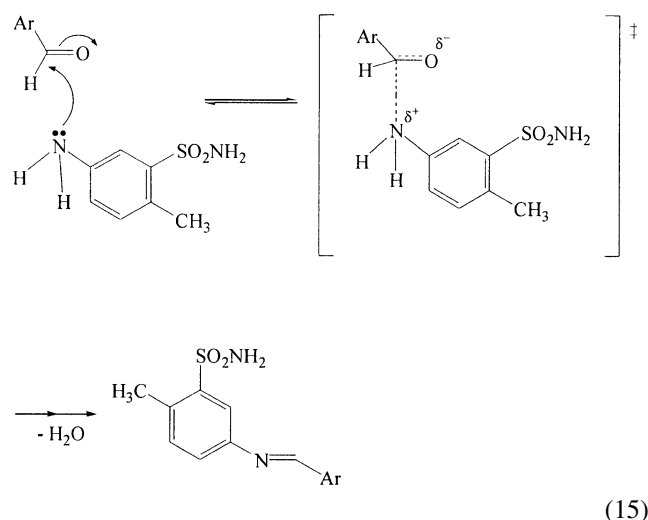
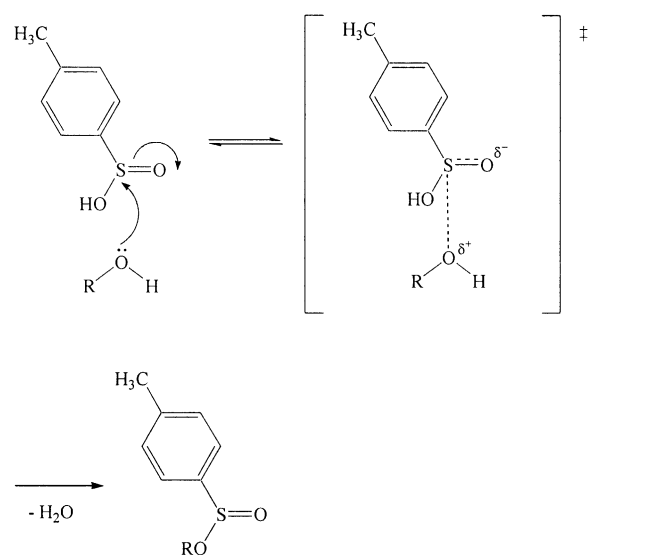


Table 8. Reaction of 5-amino-2-toluenesulfonamide with aromatic aldehydes

Ar	Time (min)	Yield (%)		
		MW (no DMF)	MW (ε DMF)	Δ (ε DMF)
<i>p</i> -NO ₂ C ₆ H ₄	1	40	98	5
<i>o</i> -ClC ₆ H ₄	2	22	90	6
5-NO ₂ 2-furyl	2	20	96	5

7.1.1.6. Synthesis of alkyl *p*-toluenesulfonates. The reactions of aliphatic alcohols with *p*-toluenesulfonic acid are accelerated by microwave irradiation under solvent-free conditions in the presence of silica gel to afford a high-yielding synthesis of *p*-toluenesulfonate esters⁶⁹ (Eq. (16)).



R = (CH₃)₂CHCH₂ 70 °C MW 1.5 min 95% Δ 30 min 10%

7.1.1.7. Leuckart reductive amination of carbonyl compounds. This reaction is well known but, unfortunately, using classical procedures is only possible under very harsh conditions (temperature 240 °C, sealed containers, long reaction times) and gives modest yields⁷⁰ (≤30%). Its difficulty constitutes a good challenge to check the effectiveness of microwave irradiation as the mechanism develops a dipolar transition state⁷¹ (Eq. (17), Table 9) and this should also favour the involvement of a microwave effect.

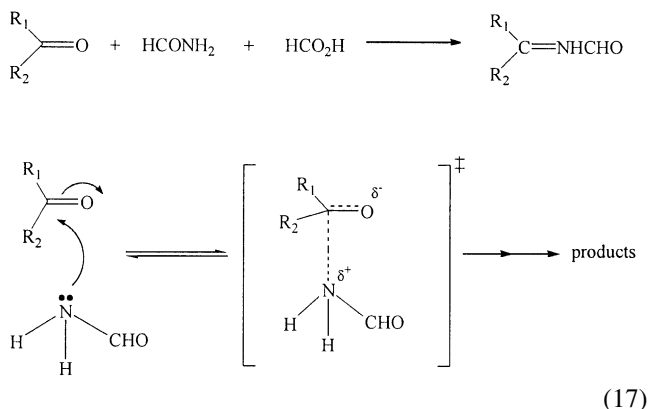
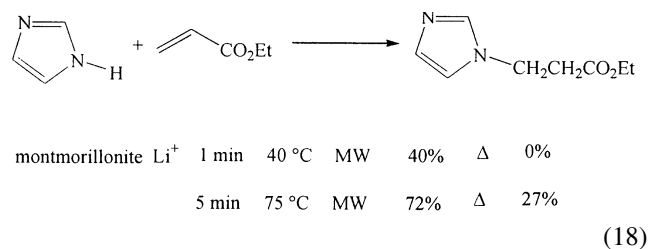


Table 9. Microwave-mediated Leuckart reductive amination of carbonyl compounds within 30 min

R ₁	R ₂	Temperature (°C)	Activation	Yield (%)
Ph	Ph	202	MW	>98
		202	Δ	2
<i>p</i> -CH ₃ OPh	<i>p</i> -CH ₃ OPh	193	MW	95
		193	Δ	3
Ph	CH ₂ Ph	210	MW	95
		210	Δ	12

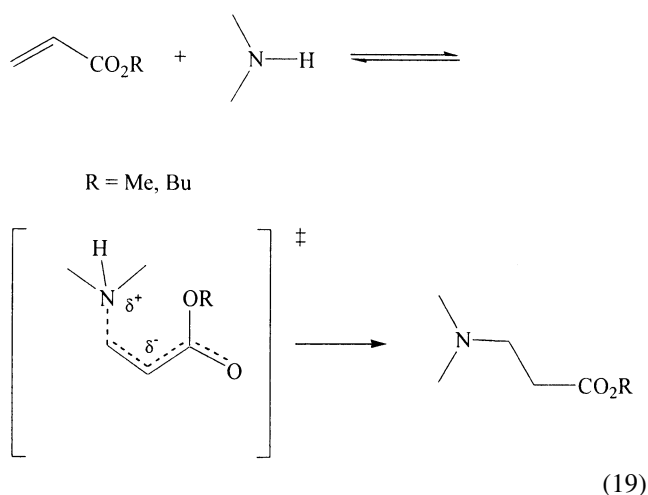
This study constitutes a distinctive example of a pronounced microwave effect for a reaction occurring with a very late dipolar transition state.

7.1.2. Michael additions. Imidazole has been condensed via a 1,4 Michael addition with ethyl acrylate using basic clays (Li⁺ and Cs⁺ montmorillonites) under solvent-free conditions with microwave irradiation⁷² (Eq. (18)).



It was shown that microwave irradiation accelerated the 1,4 Michael addition of primary and cyclic secondary amines to acrylic esters leading to several β-amino acid derivatives in

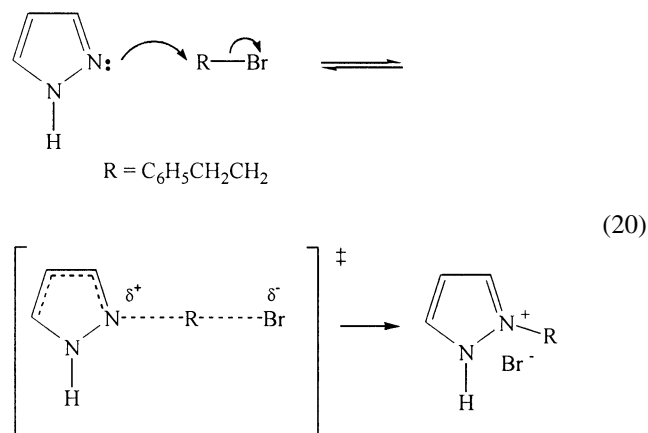
good yields within short reaction times⁷³ (Eq. (19)).



1,2 asymmetric induction of up to 76% diastereoisomeric excess was observed in the reactions of several amines with β -substituted acrylic acid esters from $D(+)$ mannitol in the absence of solvent after 12 min microwave exposure.⁷⁴

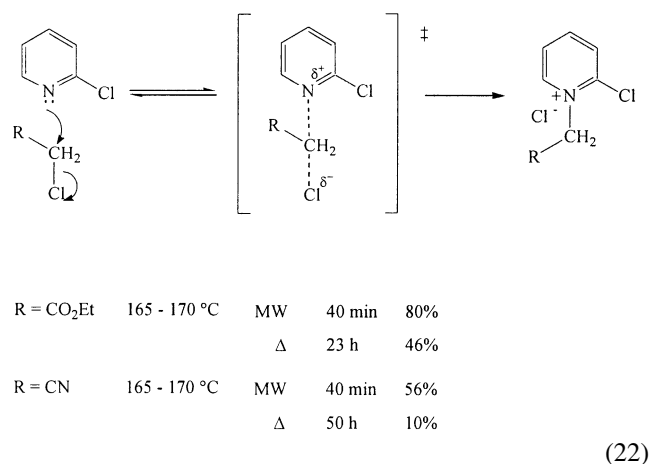
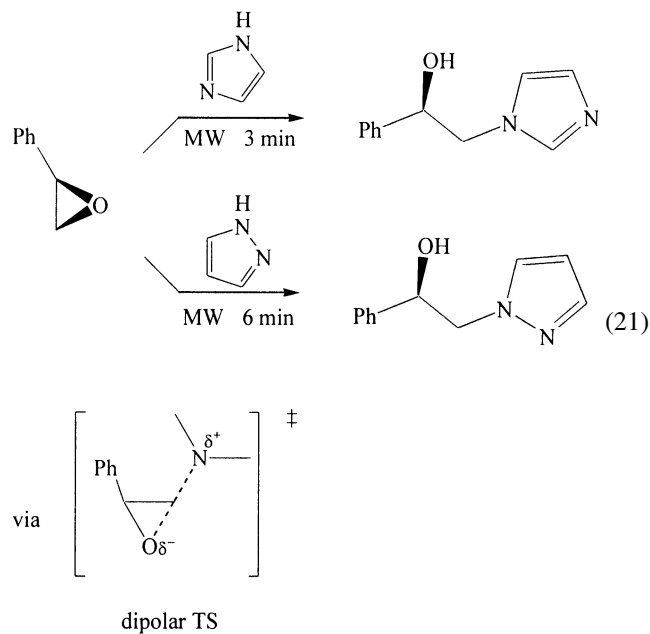
7.1.3. S_N2 reactions

7.1.3.1. Reaction of pyrazole with phenethyl bromide. In the absence of base, the phenethylation of pyrazole under solvent-free conditions is more rapid by far under microwave (8 min at 145°C) when compared to Δ which requires 48 h⁷⁵ (Eq. (20)).

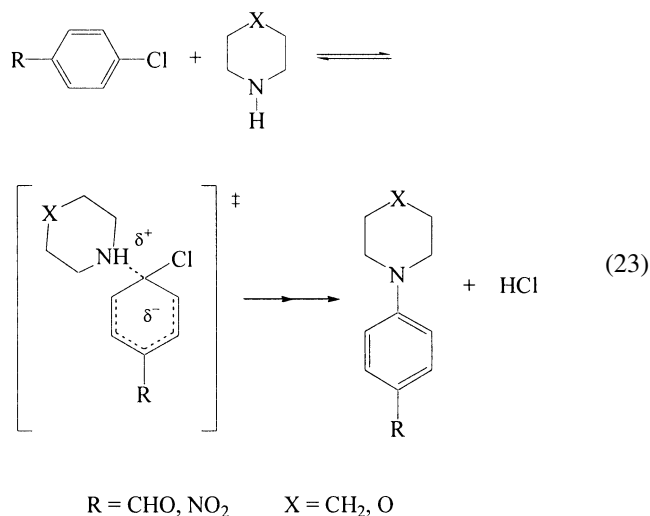


7.1.3.2. Ring opening of an epoxide by amines. Microwave-assisted ring opening of (*R*)-styrene oxide by pyrazole and imidazole leads to the corresponding (*R*)-1-phenyl-2-azolyethanols. With pyrazole, the microwave irradiation increases both the chemo- and regioselectivity compared to the conventional heating method⁷⁶ (Eq. (21)).

7.1.3.3. *N*-alkylation of 2-halopyridines. A microwave (focused waves) assisted procedure for *N*-alkylation of 2-halopyridines has been described with a noticeable microwave effect in total compatibility and agreement with a polar TS⁷⁷ (Eq. (22)).



7.1.3.4. Nucleophilic aromatic substitutions. An expeditious microwave assisted S_NAr reaction with cyclic amines has been reported for activated aromatic substrates⁷⁸ (Eq. (23)).



The reactions were performed in a heterogeneous medium using K_2CO_3 in ethanol (MW or Δ) or basic alumina in dry media to trap the hydrochloric acid formed. Due to the formation of a dipole in the TS, the microwave effect depicted in Table 10 was observed.

Table 10. S_NAr reaction between *p*-chlorotoluene and piperidine ($X=CH_2$, $R=CH_3$)

	Activation mode	Conditions		Yields (%)
$K_2CO_3/EtOH$	Δ	16 h	Reflux	60
	MW	6 min	Reflux	70
Basic alumina	MW	75 s	^a	92

^a Undetermined, but certainly a very high temperature as the vessel was placed inside an alumina bath (prone to microwave absorption).

7.1.3.5. Synthesis of phosphonium salts. Using a domestic oven, it was shown that the reaction of triphenylphosphine and an organic halide is very rapid under microwave irradiation. The reaction times were reduced to only few minutes in contrast to conventional heating which requires from 30 min to 14 days.⁷⁹

Nucleophilic substitutions of benzyl chloride or benzyltrimethylammonium chloride as electrophiles with Ph_3P or Bu_3P as nucleophiles have been carried out with accurate control of the power and temperature using a monomode reactor. The results were carefully compared under similar conditions with microwave or Δ activation⁸⁰ (Eq. (24), Table 11).

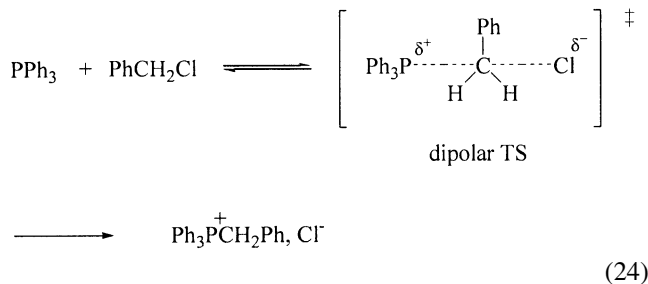


Table 11. Solvent-free benzylation of triphenylphosphine within 10 min

Temperature (°C)	Yields (%)	
	MW	Δ
100	78	24
150	94	91

Although the microwave effect is not appreciable at 150°C, it becomes clearly apparent when the temperature is decreased to 100°C. When delineating microwave effects, careful attention needs to be paid to the temperature level. If this is too high, the microwave effect will be masked and the temperature has to be minimised in order to start from a low yield under Δ and therefore have the possibility of observing microwave enhancements.

This conclusion is in agreement with the kinetic results from Radoiu et al.⁸¹ obtained for the transformation of 2- and 4-*t*-butyl phenols in the liquid phase in the presence of montmorillonite KSF as catalyst either under MW or Δ

(Eq. (25), Table 12).

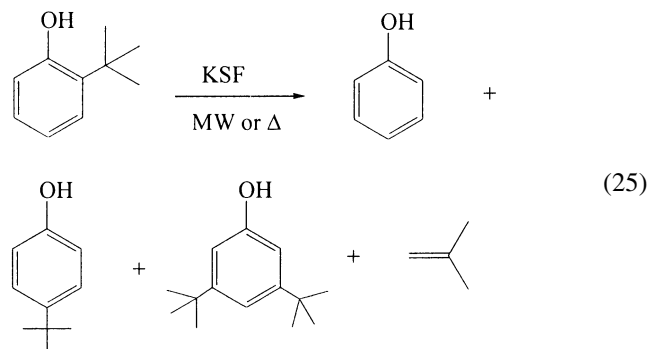
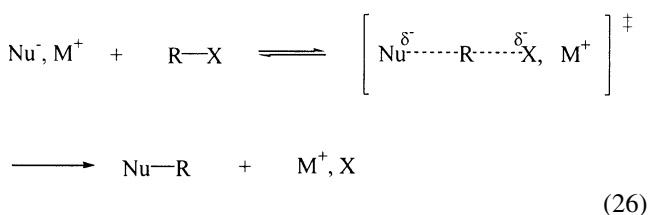


Table 12. Rate constants (r^0) for the transformation of 2-*t*-butyl phenols under MW or Δ according to temperature

Temperature (°C)	$r_{MW}^0 (\times 10^3 s^{-1})$	$r_{\Delta}^0 (\times 10^3 s^{-1})$	$r^0 (MW/\Delta)$
22	1.5	0.07	21.6
75	3.2	1.2	2.7
105	10.3	7.1	1.5
198	21.0	20.0	1.1

7.2. Bimolecular reactions with one charged reactant

The TS for anionic S_N2 reactions involves loose ion pairs in a charge delocalized (soft) anion. On the other hand, the GS could involve a neutral electrophile and either tight or loose ion pairs depending on the anion structure (hard or soft) (Eq. (26)).



7.2.1. Anionic S_N2 reactions involving charge localized anions. In this case, the anion being hard and with a high charge density, the reactions are concerned with tight ion pairs. During the course of the reaction, ionic dissociation is increased and hence polarity is enhanced from the GS towards the TS. Specific microwave effects should be expected.

7.2.1.1. Selective dealkylation of aromatic alkoxyated compounds. Selective deethylation of 2-ethoxyanisole is observed using KO^tBu as the reagent in the presence of 18-crown-6 as the phase transfer agent (PTA). With the addition of ethylene glycol (E.G.), the selectivity is reversed and demethylation occurs (Eq. (27), Table 13). If the involvement of microwaves is favourable in both examples, the second reaction should be more strongly accelerated than the first one.⁸²

Demethylation results from the S_N2 reaction whereas deethylation occurred via the $E2$ mechanism (Scheme 8).

The microwave-specific effect is more apparent in the case of demethylation (S_N2). The microwave acceleration clearly is more pronounced with the difficulty of the reaction, thus

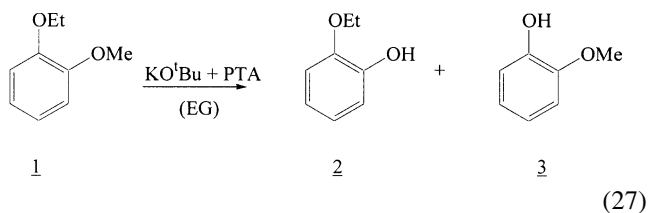
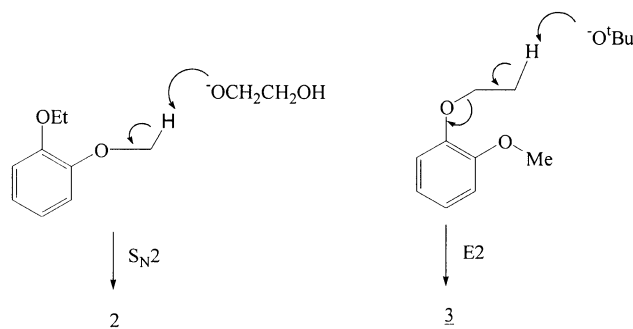


Table 13. Reaction of KO^tBu with 2-ethoxyanisole in the presence of 18-crown-6 and, optionally, ethylene glycol

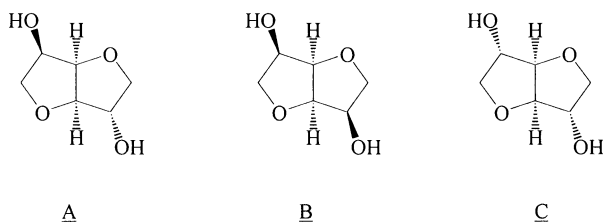
Additive	Time	Activation	Temperature (°C)	<u>1</u> (%)	<u>2</u> (%)	<u>3</u> (%)
–	20 min	MW	120	7	0	90
–	20 min	Δ	120	48	0	50
E.G.	1 h	MW	180	0	72	23
E.G.	1 h	Δ	180	98	0	0



Scheme 8. Mechanisms for demethylation and deethylation of ethoxyanisole.

constituting a clear example of an increased microwave effect with a more difficult reaction, indicative of a later TS position along the reaction coordinates. The microwave effect may also be connected to the more localized charge in the S_N2 transition state (three centres) when compared to that of β-E2 (charge developed over five centres).

7.2.1.2. Alkylation of dianhydrohexitols under PTC conditions. Dianhydrohexitols, important by-products of biomass (Scheme 9), were dialkylated under PTC conditions in the presence of a small amount of xylene.



Scheme 9. Structure of 1,4:3,6-dianhydrohexitols (A=isosorbide, B=isomannide, C=isoidide).

Dialkylations were attempted as model reactions before subsequent polymerisations and revealed very important specific microwave effects⁸³ (Eq. (28), Table 14).

These observations are consistent with the reactive species being constituted from tight ion pairs between cations and

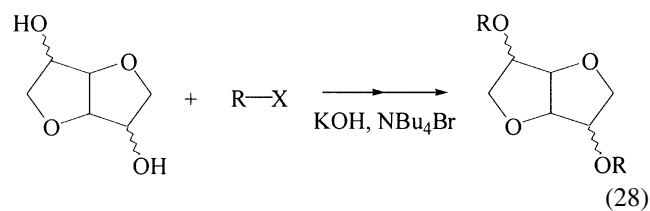
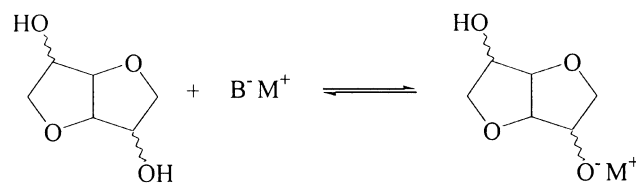


Table 14. Dialkylation of dianhydrohexitols under PTC conditions

RX	<i>t</i> (min), <i>T</i> (°C)	Yield (%)					
		<u>A</u>		<u>B</u>		<u>C</u>	
		MW	Δ	MW	Δ	MW	Δ
PhCH ₂ Cl	5, 125	98	13	98	15	97	20
<i>n</i> C ₈ H ₁₇ Br	5, 140	96	10	74	10	95	10

the alkoxide anions resulting from abstraction of hydrogen atoms in A, B and C (Scheme 10).



Scheme 10.

The reaction of monobenzylated isosorbide D with ditosylates (Eq. (29)) is more subtle; the microwave-specific effect (Table 15) appeared when the temperature was lowered to 80°C (modulated by the presence of cyclohexane) whereas it was masked by a higher temperature of 110°C (maintained by the use of toluene).⁸⁴

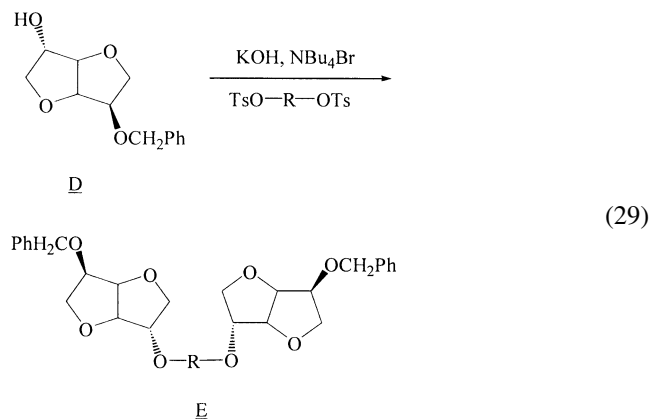
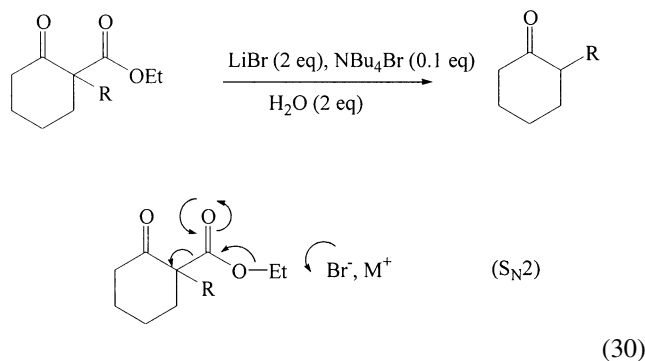


Table 15. Reaction of monobenzylated isosorbide (D) with ditosylates for 15 min

R	Yields (% <u>E</u>)			
	<i>T</i> 110°C (xylene)		<i>T</i> 80°C (cyclohexane)	
	MW	Δ	MW	Δ
(CH ₂) ₈	95	91	96	39
(CH ₂) ₆	91	90	96	45
CH ₂ CH ₂ OCH ₂ CH ₂	92	92	91	36

7.2.1.3. Krapcho reaction. Dealkoxycarbonylation of activated esters occurs classically under drastic thermal conditions.⁸⁵ It constitutes a typical example of a very slow-reacting system (with a late TS along the reaction coordinates) and is therefore prone to a microwave effect. The rate determining step involves a nucleophilic attack by halide anion and requires anionic activation, which can be provided by solvent-free PTC conditions under microwave irradiation.⁸⁶ The above results illustrate the difficult example of cyclic β -ketoesters with a quaternary carbon atom in the α position relative to each carbonyl group (Eq. (30)).

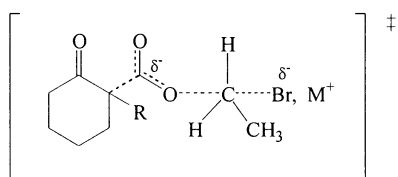


Some typical results are summarized in Table 16.

Table 16. Krapcho reaction under solvent-free PTC conditions

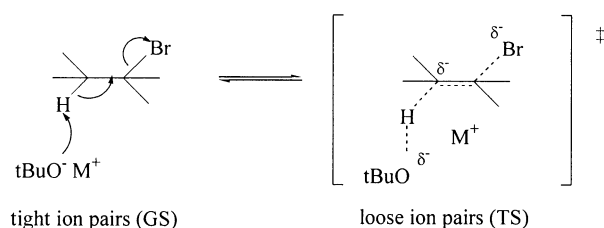
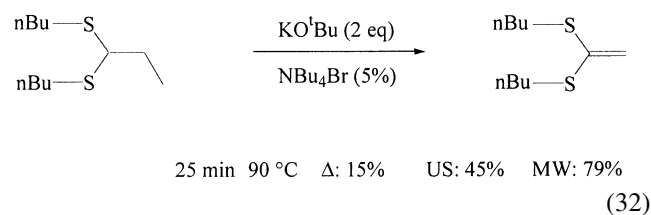
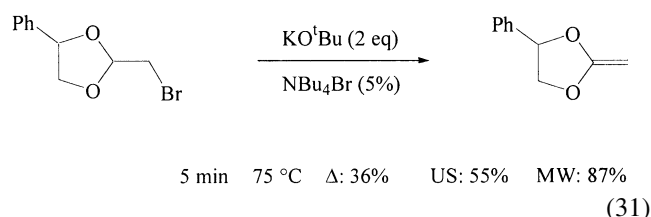
R	Reaction conditions		Yields (%)	
	<i>t</i> (min)	Temperature (°C)	MW	Δ
H	8	138	96	<2
Et	15	160	94	<2
<i>n</i> -Bu	20	167	89	<2
<i>n</i> -Hex	20	186	87	<2
	60	186		22
	180	186		60

A definite microwave effect is involved when strict comparisons of MW and Δ activation are considered and is compatible with the mechanistic assumption that a very polar TS is developed (Scheme 11).



Scheme 11. Transition state for the Krapcho reaction.

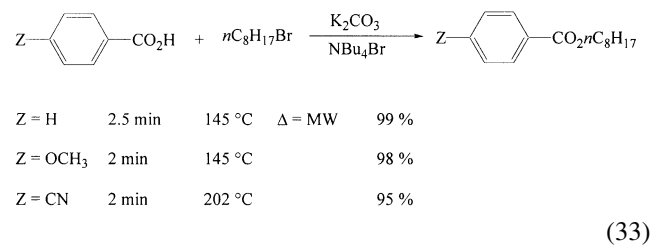
7.2.1.4. Anionic β -elimination. Ketene acetal synthesis by β -elimination of haloacids from halogenated acetals under well controlled conditions using thermal activation (Δ), ultrasound (US) or microwave irradiation⁸⁷ (MW) has been described. From a mechanistic point of view, as the TS is more charge delocalized than the GS and the polarity is enhanced during the course of the reaction, a favourable microwave effect can therefore be observed (Eqs. (31) and (32)) (Scheme 12).



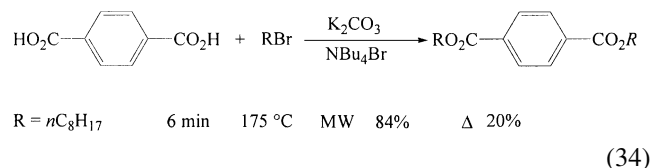
Scheme 12. Evolution of polarity in β -elimination.

7.2.2. Anionic S_N2 reactions involving charge delocalized anions. Weak or non-existent microwave effects are expected for these reactions as the GS and TS exhibit rather similar polarities since they both involve loose ion pairs.

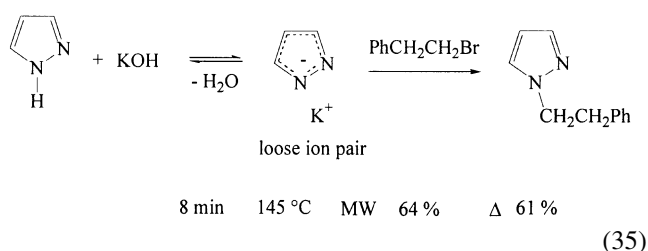
7.2.2.1. Alkylation of potassium benzoate. Alkylation of several substituted benzoic acid salts with *n*-octyl bromide was performed under solvent-free PTC with excellent yields ($\geq 95\%$) within a very short reaction time⁸⁸ (2–7 min). Oil bath heating (Δ) led to yields equivalent to those produced under microwave irradiation, which thus revealed only thermal effects in the range of temperature used (145–202°C) (Eq. (33)).



Conversely, when *n*-octyl bromide was used with the less reactive terephthalate species, which constitutes a 'slow-reacting system', the yield was raised from 20 to 84% under microwaves compared to Δ which can be attributed to a later TS along the reaction coordinates (Eq. (34)).



7.2.2.2. Pyrazole alkylation in basic media.⁷⁵ A very important microwave-specific effect was evidenced in the absence of a base for the reaction of pyrazole with phenethyl bromide (reaction times: MW=8 min, Δ =48 h, Eq. (35)). When the same reaction was carried out in the presence of KOH, the microwave effect disappeared (vide supra Eq. (20)).



This effect could be predicted when considering the weak evolution of polarity between the GS and TS as the reactive species consist of loose ion pairs (involving a soft anion).

7.2.2.3. Selective alkylation of β -naphthol in basic media. Alkylations in dry media of the ambident 2-naphthoxide anion were performed under focused microwave activation. Whereas the yields were identical to those obtained under Δ for benzoylation, they were significantly improved under microwave irradiation conditions for the more difficult *n*-octylation (a less reactive electrophilic reagent). No change in selectivity was observed, however, indicating the lack of influence of ionic polarization.⁸⁹

The absence or weakness of the microwave effect was assumed to be related to loose ion pairs involving the soft naphthoxide anion in the GS and a small change in polarity in an early TS. When the TS occurred later along the reaction coordinates (e.g. for *n*-octylation requiring a higher temperature), more polarity is developed and, consequently, the microwave effect could appear (Eq. (36) and Table 17 limited here to the lithiated base).

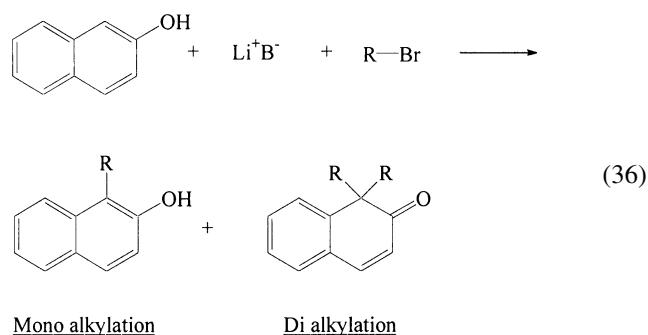


Table 17. C-alkylation of β -naphthol in the presence of lithiated base under solvent-free conditions

RX	Li ⁺ B ⁻	<i>t</i> (min)	Temperature (°C)	Yield (%)			
				MW Mono C	MW Di C	Δ Mono C	Δ Di C
PhCH ₂ Br	LiOH	4	190	98	2	97	2
	LiO ^t Bu	4	137	9	91	8	88
<i>n</i> C ₈ H ₁₇ Br	LiOH	9	240	92	1	62	–
	LiO ^t Bu	10	200	27	56	7	20

7.2.3. Nucleophilic additions to carbonyl compounds

7.2.3.1. Saponification of hindered aromatic esters. This is a typical representative example of an enhanced microwave-specific effect related to the difficulty of the reaction, which presumably proceeds via a later and later TS. Whereas essentially thermal effects are observed (around 200°C) with methyl and octyl benzoate, a microwave-specific effect is increasingly apparent with hindered esters and becomes optimal with mesitoyl octanoate (Eq. (37), Table 18).⁹⁰

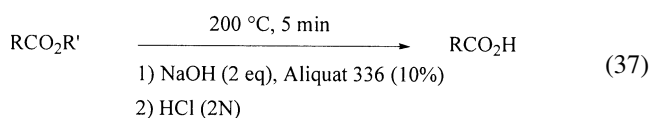


Table 18. Solvent-free PTC saponifications of aromatic esters

R	R'	Yield (%)	
		MW	Δ
Ph	Me	92	73
Ph	<i>n</i> Oct	98	86
	Me	90	48
	<i>n</i> Oct	97	39

7.2.3.2. PTC transesterification in basic medium. The microwave-assisted PTC transesterification of several carbohydrates in basic medium with methyl benzoate or laurate has been studied.⁹¹ Small amounts of DMF were necessary to provide good yields within 15 min at 160°C. Rate enhancements were compared to conventional heating (Δ) under the same conditions and specific microwave activation was mostly seen when the less reactive fatty compounds were involved (Eq. (38), Table 19)

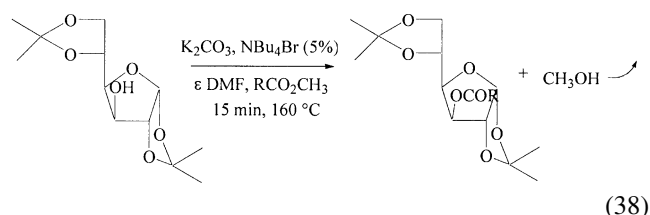


Table 19. Transesterification in basic medium with methyl benzoate and laurate within 15 min at 160°C (monomode reactor, relative amounts 1:2:2)

R	Yield (%)		
	MW	Δ	
Ph	96	21	
CH ₃ (CH ₂) ₁₀	88	0	

The reactive species under these conditions consist of tight ion pairs involving the alkoxide anion from the carboxylate (charge localized anion). The less reactive long chain methyl laurate leads to a later TS along the reaction coordinates and the magnitude of the microwave effect is therefore increased.

7.2.3.3. Ester aminolysis in basic medium. Ester aminolysis, in general, occurs under harsh conditions that require high temperatures and extended reaction periods or the use of strong alkali metal catalysts. An efficient solid-state synthesis of amides from non-enolizable esters and amines using KO^tBu under microwave irradiation⁹² has been described. The reaction of esters with octylamine was extensively studied to identify possible microwave effects⁹³ (Eq. (39), Table 20).

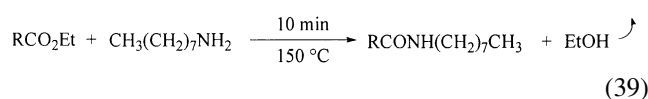
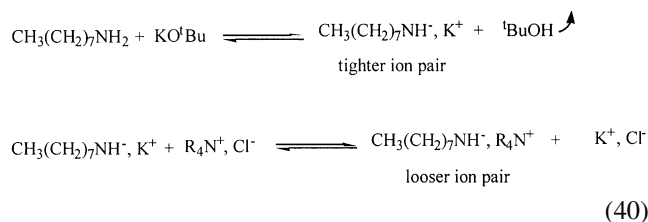


Table 20. Ester aminolysis with *n*-octylamine at 150°C for 10 min

R	Base	Yield (%)	
		MW	Δ
Ph	–	0	0
	KO ^t Bu	80	22
	KO ^t Bu+Aliquat 336	87	70
PhCH ₂	–	63	6
	KO ^t Bu+Aliquat 336	63	36

The microwave-specific effect is increased when the reaction is performed in the absence of a phase transfer catalyst, showing that the nature of the reactive species is of great importance in connection with ionic dissociation (Eq. (40)).



As expected, the tighter ion pair (RNH[−], K⁺) exhibits the larger microwave effect. As an extension of this work, and in order to gain further insight, the effect of amine substituents was studied⁹⁰ in the reaction with ethyl benzoate (Eq. (41), Table 21).

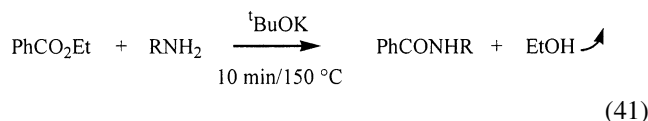


Table 21. Ethyl benzoate aminolysis with different amines at 150°C for 10 min (relative amounts PhCO₂Et/RNH₂/KO^tBu=1.5:1:2)

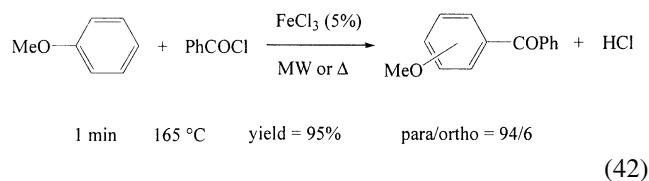
R	Yield (%)		With NR ₄ Cl yield (%)	
	MW	Δ	MW	Δ
Ph	88	73	90	83
PhCH ₂	84	42	98	85
<i>n</i> Oct	80	22	87	70

The microwave effects are clearly substituent dependent and, as in the former example, disappear by adding a PTA. When the substituent R is able to delocalise the negative charge on the amide anion (R=Ph), the ion pairs RNH[−], M⁺ exist in a looser association. Consequently, a decrease in microwave effect is expected as the evolution from the GS→TS occurs with only a slight modification of polarity in the ion pairs. Conversely, the microwave effect is optimal with the tighter ion pair (*n*OctN[−], K⁺).

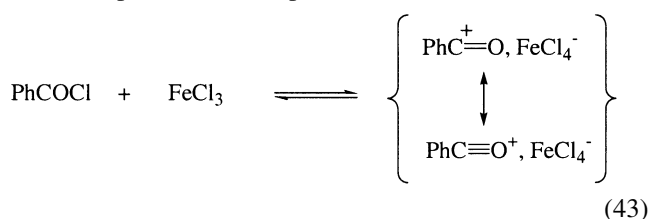
7.2.4. Reactions involving positively charged reactants. Relatively few comparative MW/Δ studies are presently available in this area.

7.2.4.1. Friedel–Crafts acylation of aromatic ethers.

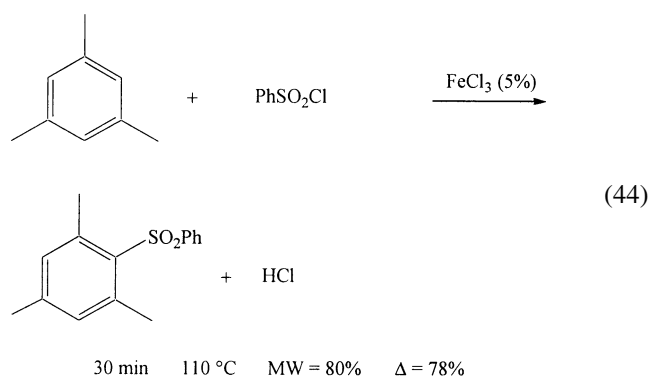
Solvent-free benzylation of aromatic ethers has been carried out under microwave irradiation in the presence of a metallic catalyst, FeCl₃ being one of the most efficient.⁹⁴ With careful control of the temperature and other parameters, non-thermal microwave effects have not been observed either in terms of yields or isomeric ratios of the obtained products (Eq. (42)).



The reactive species is the acylium ion resulting from abstraction of a chloride anion from benzoyl chloride (Eq. (43)). This reagent comprises an ion pair formed between two large (soft) ions which are therefore associated as loose ion pairs. According to these assumptions, the absence of a microwave effect should be expected as the polarity evolution is very weak between the GS and TS (two loose ion pairs of similar polarities).



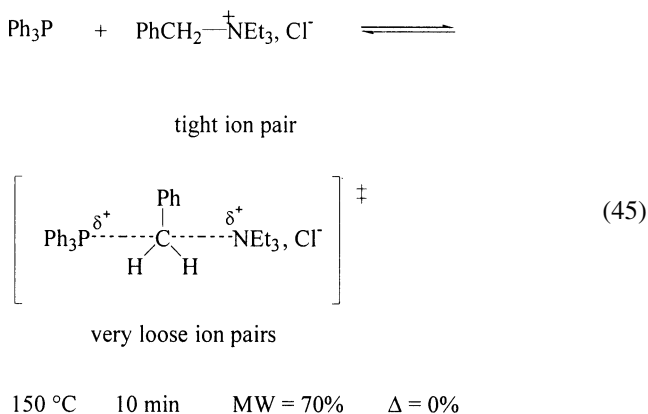
This conclusion is also in agreement with the results obtained for the sulfonylation of mesitylene in the presence of metallic catalysts such as FeCl₃⁹⁵ (5%) (Eq. (44)).



A non-thermal microwave effect was not observed when identical temperature gradients were produced by classical heating and microwave irradiation and if the reaction temperature was strictly controlled.

7.2.4.2. S_N2 reactions with tetralkylammonium salts.

The S_N2 reaction of triphenylphosphine with triethylbenzylammonium chloride (the tertiary amine is thus the leaving group) was studied under solvent-free microwave conditions. The reaction occurred only under MW⁸⁰ irradiation (Eq. (45)).



This effect may readily attributed to the very loose structure of the ion pairs in the TS (additionally involving delocalisation in the phenyl groups of the phosphine) and which are therefore far more polar than the initial ion pairs in the GS.

7.3. Unimolecular reactions

7.3.1. Imidization reaction of a polyamic acid.²³ The polyamic acid (Fig. 7) precursor was prepared by adding stoichiometric amounts of 3,3',4,4'-benzophenonetetracarboxylic acid dianhydride (BTDA) and diaminodiphenylsulfone (DDS). The solution in NMP was then submitted to either thermal or MW activation with accurate monitoring of the temperature (Scheme 13).

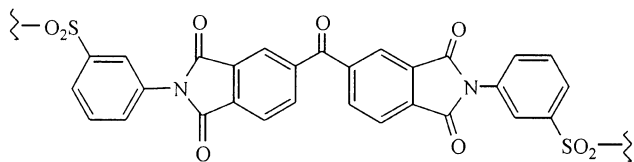
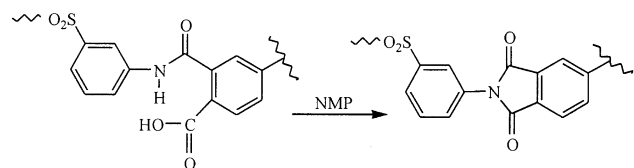


Figure 7.



Scheme 13.

Analysis of the kinetic parameters showed that the apparent activation energy for the reaction was reduced from 105 to 57 kJ/mol (Table 4). This observation is consistent with the

polar mechanism of this reaction implying the development of a dipole in the transition state (Fig. 8) even when the reaction was carried out in a polar solvent.

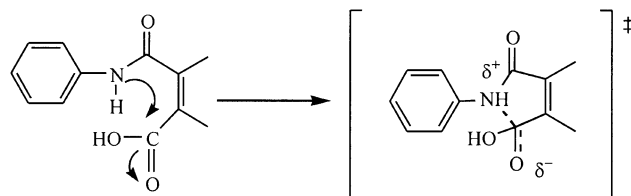


Figure 8. Mechanism for the imidization reaction.

7.3.2. Cyclisation of monotrifluoroacetylated *o*-arylenediamines.

Cyclocondensation of *N*-(trifluoroacetamido)-*o*-arylenediamines leads to a series of 2-trifluoromethyl-aryl-imidazoles with good yields on montmorillonite K10 in dry media under microwave irradiation within 2 min. Using conventional heating under the same conditions, no reaction was observed⁹⁶ (Eq. (46), Table 22).

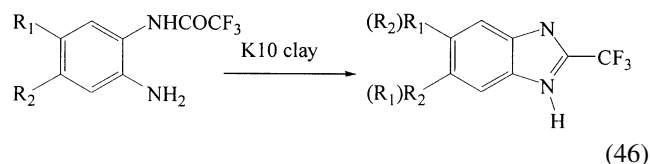
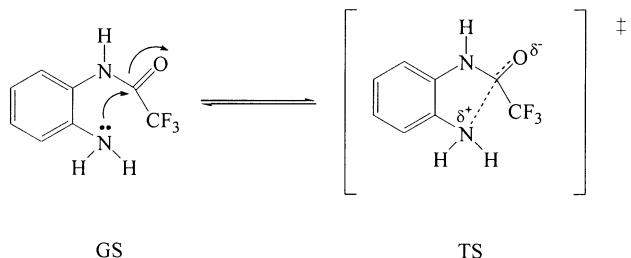


Table 22. Cyclisation of monotrifluoroacetylated *o*-arylenediamines

R ₁	R ₂	Temperature (°C)	Yield (%)	
			MW (2 min)	Δ (20 h)
H	H	125	87	23
H	CH ₃	127	84	19
NO ₂	H	134	95	28

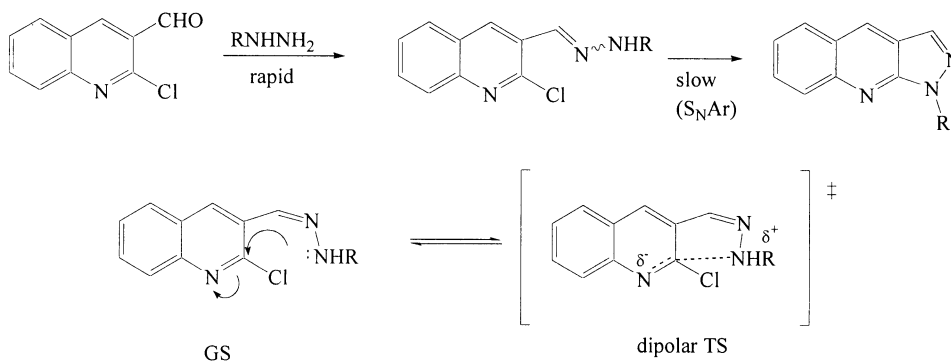
This observation is consistent with the assumptions of the authors predicting microwave effects when the polarity is enhanced in a dipolar TS. The kinetic rate-determining step consists of an intramolecular attack of the nitrogen lone pair on the carbon atom of the carbonyl moiety (Scheme 14).



Scheme 14. Mechanism for cyclocondensation.

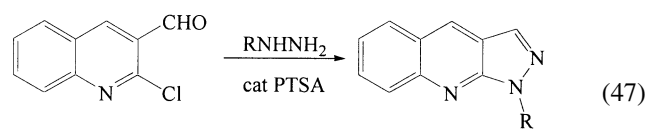
7.3.3. Intramolecular nucleophilic aromatic substitutions.

Pyrazolo[3,4*b*]-quinolines and -pyrazoles have been synthesized by reacting β-chlorovinylaldehydes and hydrazine or phenyl hydrazine using a catalytic amount of *p*-toluenesulfonic acid (PTSA) under microwave irradiation. The yields are much better than under Δ using the same



Scheme 15. Mechanism of internal S_NAr . (R=H, Ph).

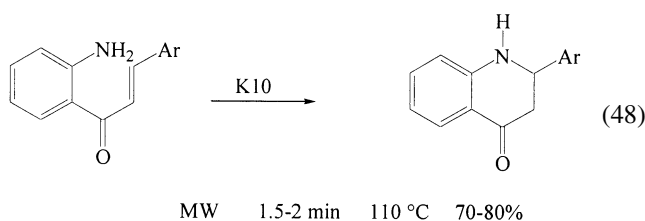
conditions⁹⁷ (Eq. (47)).



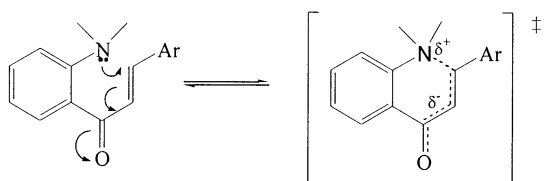
R = H 1.5 min 127–130 °C MW = 97% Δ = 30%

The noticeable rate enhancement due to a microwave-specific effect is consistent with a reaction mechanism in which the kinetic rate-determining step is nucleophilic attack of an amino group on the chloroquinoline ring (Scheme 15).

7.3.4. Intramolecular Michael additions. *ortho*-Amino-chalcones were cyclised to tetrahydroquinolones in dry media using K10 clay as the support under microwave irradiation. The role of microwaves in accelerating the process was evidenced as a relatively extended reaction time was required under conventional heating to obtain similar yields⁹⁸ (Eq. (48), Scheme 16).



MW 1.5–2 min 110 °C 70–80%



Scheme 16. Mechanism of intramolecular Michael addition of an amino group.

A similar study has been reported with *ortho*-hydroxy-chalcones in dry media in silica gel.⁹⁹ Conventional thermal cyclisation, under the same conditions as for microwave irradiation, required a much longer reaction period (Eq.

(49), Table 23, Scheme 17).

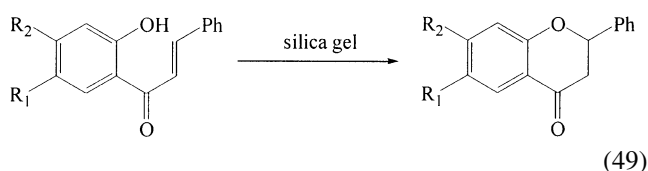
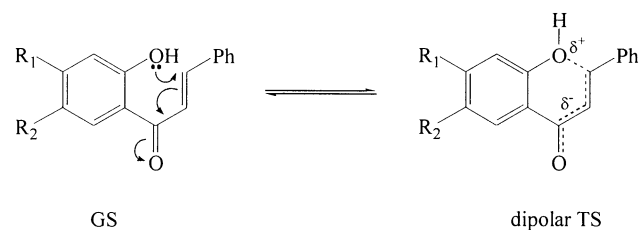


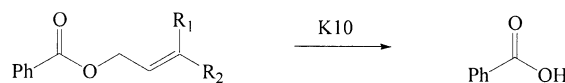
Table 23. Intramolecular Michael addition of *o*-hydroxychalcones during 20 min at 140 °C

R ₁	R ₂	Mode	Yield (%)
H	H	MW	82
		Δ	44
CH ₃ O	H	MW	61
		Δ	22



Scheme 17. Mechanism of intramolecular Michael addition of an hydroxy group.

7.3.5. Deprotection of allyl esters. Carboxylic acids are regenerated from their corresponding substituted allyl esters on montmorillonite K10 using microwave irradiation under solvent-free conditions to afford enhanced yields and reduced reaction times when compared to thermal conditions¹⁰⁰ (Eq. (50)).

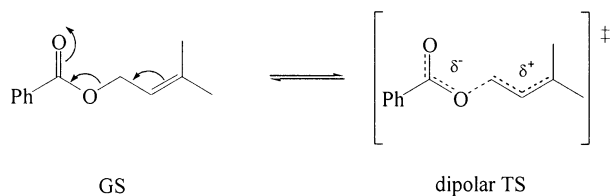


R₁ = H R₂ = Ph 110 °C MW : 20 min 96% Δ : 6 h 96%

R₁ = R₂ = H 110 °C MW : 20 min 98% Δ : 5 h 94%

(50)

This effect can also get again be rationalized via a mechanism with the intervention of a more polar TS (Scheme 18).



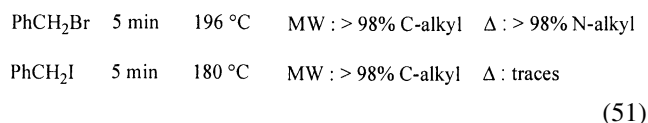
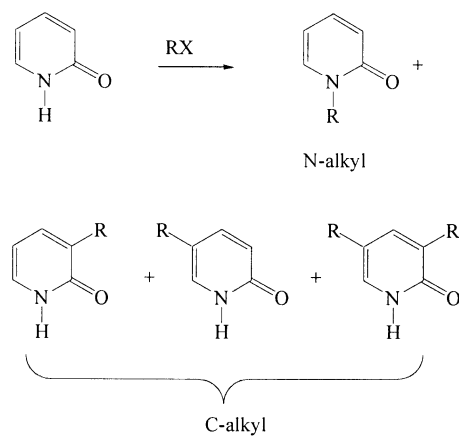
Scheme 18. Mechanism of deprotection of allyl esters.

8. Some illustrative examples of the effects on selectivities

Very few results on selectivity effects are available due to a lack of strict comparisons between microwave and Δ activation and in which kinetic details of reactions have been described. Reports of the effect of microwaves on selectivity up to 1997 have been reviewed by Langa et al.⁶⁰

8.1. Benzylation of 2-pyridone

Regiospecific *N*- or *C*-benzylations of 2-pyridone were observed under solvent-free conditions in the absence of base. The regioselectivity was controlled by the activation method (MW or Δ) or, when using microwaves, by the emitted power level or the leaving group of the benzyl halides⁵⁸ (Eq. (51)).

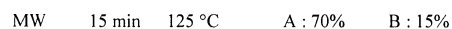
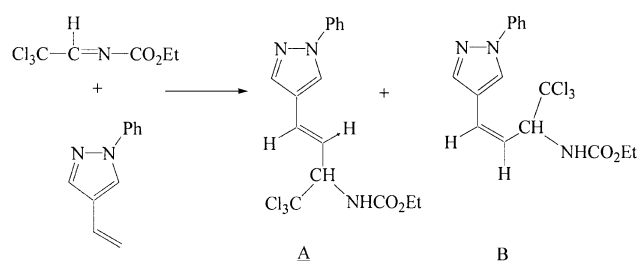


In order to justify these results, it may be assumed that the TS leading to *C*-alkylation will be more polar than that responsible for *N*-alkylation. This assumption, however, presumes the existence of kinetic control (which is non-ensured in this case).

8.2. Addition of vinylpyrazoles to imine systems

Upon microwave irradiation, vinylpyrazoles react with *N*-trichloroethylidene carbamate to undergo addition to the imine system through the conjugated vinyl group¹⁰¹

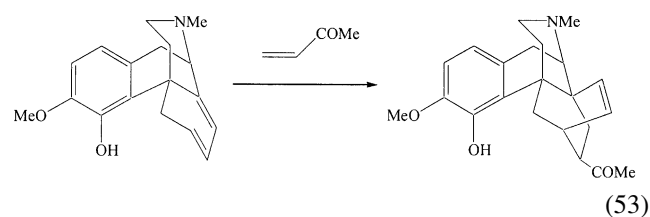
(Eq. (52)).



(52)

The use of microwave irradiation as an energy source is crucial to conduct the reaction and to avoid the decomposition or dimerization of the starting pyrazole, which are observed in the absence of microwave irradiation.

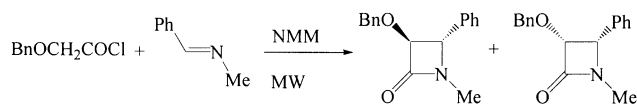
A similar conclusion has been drawn during an examination of the Diels–Alder reaction of 6-demethoxy- β -dihydrothebaine with methylvinylketone using microwave irradiation.¹⁰² When performed under conventional heating conditions, extensive polymerisation of the dienophile was observed whereas reaction is much more cleaner under microwave activation (Eq. (53)).



(53)

8.3. Stereo control of β -lactam formation^{103,104}

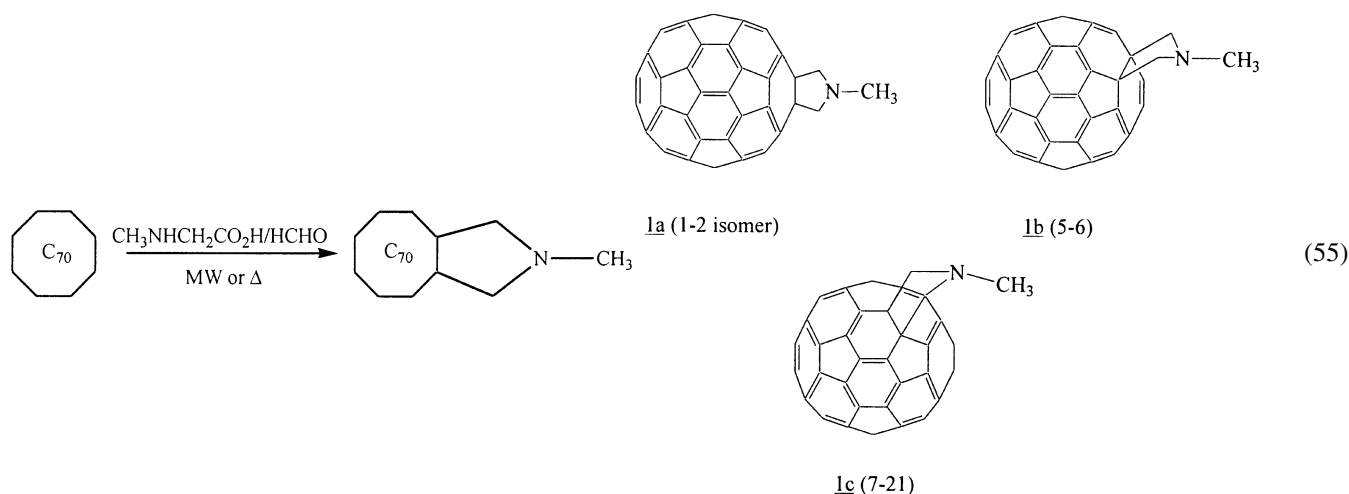
Formation of β -lactams by the reaction of an acid chloride, a Schiff base and a tertiary amine (Eq. (54)) appears to involve multiple pathways, some of which are very fast at higher temperatures. When conducted in open vessels in unmodified microwave ovens, high level irradiation leads to preferential formation of the *trans*- β -lactams (55%) whereas, at low power, the *cis*-isomer was obtained as the only product (84%). The failure of the *cis*-isomer to isomerise to the *trans*-compounds is an example of induced selectivity.



NMM = N-methylmorpholine

(54)

The transition state leading to the *trans*-isomer therefore seems to be more polar than that leading to the *cis*-compound.



8.4. Cycloaddition to C₇₀ fullerene

The regioselectivity of the cycloaddition of *N*-methylazomethine ylide to C₇₀ was claimed to be slightly affected using microwave irradiation as the source. By choosing an appropriate solvent (*o*-dichlorobenzene, ODCB) and the emitted microwave power, the ratio *1a/1b* is modified

Table 24. Yields of monoadducts and isomer distribution for cycloaddition (Eq. (55)) in ODCB at 180°C

Mode	Time (min)	Yields (%)	% <u>1a</u>	% <u>1b</u>	% <u>1c</u>
MW	120 W	30	39	50	50
	180 W	30	37	45	55
	300 W	15	37	47	53
Δ	120	32	46	46	8

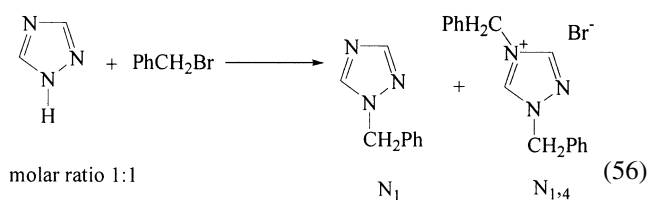
from 50:50 to 45:55^{27,61} (Table 24, Eq. (55)).

Theoretical calculations predict an asynchronous mechanism and suggest that the modification of the regiochemical outcome is related to the energies and hardness of the TS involved. Perhaps, in other words, the more polar TS are favoured under MW.

8.5. Selective alkylation of 1,2,4-triazole

Using MW irradiation under solvent-free conditions, it was possible to obtain regiospecific benzylation in position 1 of 1,2,4-triazole whereas only the 1,4-dialkylated product was

obtained in poor yields under conventional heating¹⁰⁵ (Eq. (56)).



5 min	165 °C	MW: yield 70%	100% N ₁
		Δ: yield 14%	100% N _{1,4}

This observation may be explained by the increased efficiency of the first benzylation (S_N2 reaction between two neutral reagents proceeding via a dipolar TS) under microwave conditions.

As an extension towards azolic fungicides, phenacylation was next examined. Under microwave irradiation, exclusive reaction in position 1 (or equivalent 2) occurred whereas mixtures of N₁, N₄ and N_{1,4} products were obtained by Δ under the same conditions¹⁰⁶ (Eq. (57), Table 25).

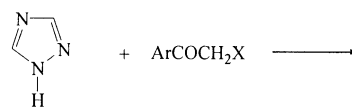
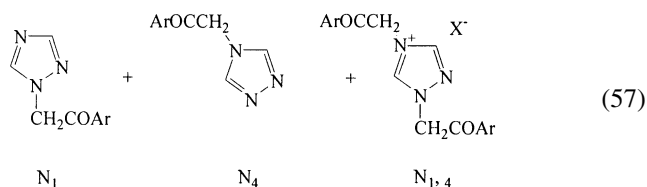


Table 25. Phenacylations of 1,2,4-triazole

Ar	X	Time (min)	Temperature (°C)	Mode	Global yield (%)	N ₁	N ₄	N _{1,4}
	Cl	25	140	MW Δ	90 98	100 33	– 29	– 38
	Cl	20	140	MW Δ	95 98	100 38	– 27	– 37
	Br	24	170	MW Δ	90 98	100 38	– 28	– 34

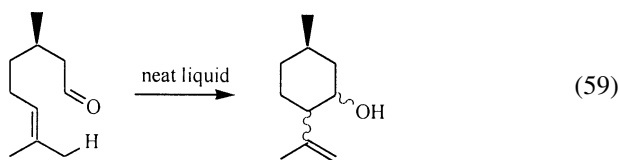
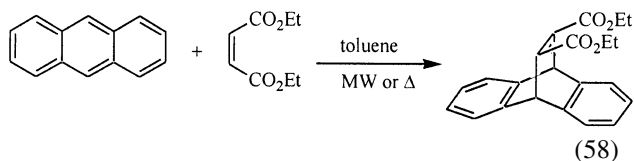


As kinetic control was ensured, this clear microwave effect could possibly be due to a difference in polarity of the transition states, with apparently a more polar TS being formed when π attack by the nitrogen atom in position 2 is concerned. Theoretical calculations are in progress at the present time to try to confirm this assumption.

9. Concerning the absence of microwave effects

The absence of a microwave effect can result from at least three different origins:

(a) a similar polarity of the transition state when compared to the ground state. This is the situation for synchronous mechanisms in some pericyclic reactions when performed in non-polar solvents^{4,5} or in neat liquids (Eqs. (58) and (59)).



(b) a very early transition state along the reaction coordinates (cf Hammond postulate) which cannot allow the development of polarity between the GS and TS (reactant-like). This will occur when the reactions are rather easy and do not require classically harsh conditions. This would be true for phthalimide syntheses by reacting phthalic anhydride and amino compounds,¹⁰⁷ and chalcone syntheses by reacting aromatic aldehydes and acetophenones,¹⁰⁸ etc. Slight differences can appear when performing the reaction in the presence of a solvent due to a superheating effect if no stirring is used and

(c) a too high temperature level, which may produce good yields in short reaction times under conventional heating. In order to find evidence of microwave effects, it is necessary to reduce the temperature under conventional conditions in order to start from a rather poor yield (<30–40%) to appreciate possible microwave activation. These cases have been revealed in some studies where a microwave effect appeared at relatively low temperatures but are masked at higher temperatures where yields of conventionally heated reactions are elevated.^{80,81,84}

10. Conclusions

We have proposed in this review a rationalization of microwave effects in organic synthesis based on medium effects and mechanistic considerations. If the polarity of a system is enhanced from the ground state to the transition state, it can result in acceleration due to an increase in material-wave interactions during the course of the reaction. The most frequently encountered cases concern unimolecular or bimolecular reactions between neutral molecules (as dipoles are developed in the TS) and anionic reactions of tight ion pairs i.e. involving charge localized anions (leading to ionic dissociation in TS). They could be more important in the cases of a product-like TS in agreement with the Hammond postulate. By far the most useful situation is related to solvent-free conditions (green chemistry procedures) as microwave effects are not masked or limited by solvent effects, although of course, non-polar solvents can always be used. Many types of carefully controlled experiments need to be performed, however, to evaluate the reality and limitations of this approach in order to make valid comparisons.

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Biographical sketch



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