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Microwave Activation in Phase Transfer Catalysis

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The first applications of microwave ovens in organic synthesis began very recently. In the first experiments, Gedye, and then Giguere, provided evidence for dramatic accelerations in some classical organic reactions, and these were ascribed to temperature and pressure effects, when performed in closed Teflon® vessels.[1,2] Since solvents were used in these experiments, some problems with safe operation appeared, and explosions sometimes resulted. Further developments demonstrated the potential of solvent-free reactions to solve these problems and to facilitate the scale-up of preparative runs.

Three types of solvent-free procedures can be coupled with microwave activation :[3]

i) Reactions between neat reactants, needing at least one polar molecule, as liquid-liquid or liquid-solid systems. In this latter case, reactions presumably occur at the interface due to adsorption of the liquid reactant at the surface of the solid one.[4]

ii) Reactions between supported reagents on solid mineral supports in « dry media » by impregnation of compounds on alumina, silicas or clays.[5]

iii) Phase Transfer Catalysis (PTC) conditions in the absence of organic solvent, i. e. when a liquid reagent acts both as a reactant and an organic phase.[3] This last methodology can also be improved under sonochemical activation.[6]

I - MICROWAVE ACTIVATION

Microwaves are a form of electromagnetic radiation with a frequency of 2450 MHz fixed by law, corresponding, in vacuum, to a wavelength of 12.2 cm. Many industrial, scientific, medical and domestic applications exist for these radiations.[7]

When molecules with a permanent dipole are submitted to an electric field, they become aligned. If this field oscillates, the orientation changes at each alternation. The strong agitation, provided by the reorientation of molecules, in phase with the electrical field excitation, causes an intense internal heating, up to 10°C per second, when powerful waves are used.

1. Advantages and Interest

Microwaves constitute a very original procedure for heating materials, clearly different from the classical ways. Their main advantages derive from the almost instantaneous "in core" heating of materials, in an homogeneous and selective manner, especially those with poor heat conduction properties. This technique proves to be excellent in cases where traditional heating has a low efficiency because of poor heat transmission, and hence local overheating is a major inconvenience.

The main interests can thus be listed as the rapid transfer of energy into the bulk of the reaction mixture, without inertia since only the product is heated, and the ease of utilization. Furthermore, as the depth of penetration in materials is of the same order of magnitude as the wavelength, microwaves interact with substances of appreciable thickness (about 10 cm).[7]

2. Applications in Organic Synthesis

By exposure to microwaves, the thermal effects undergone by materials exhibit an increased magnitude with the polarity increase of the substrate. These effects can appear in liquid systems,[8] and in

the solid state as well,[9] where structural modifications can also occur concomitantly.[10] In the presence of polar solvents, organic reactions require closed Teflon^R vessels to avoid volatilization.

The resultant advantages in comparison to classical heating are especially spectacular. Reactions are very rapid and usually complete after a few minutes, as a result of both temperature and pressure effects and supposed specific effects of the radiation, such as improved homogeneity in temperature, a faster temperature rise,[11] and possible modifications of activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[12,13] It is also generally observed that the purity of products is improved due to the shorter reaction period at high temperature and the absence of local overheating on the reactor walls which occurs under conventional heating.[4a,5]

3. Coupling with PTC Techniques [4,9,14,15]

After ion exchange, the nucleophilic ion pair $R_4N^+Nu^-$ is a highly polar species, especially prone to undergo specific microwave activation, as exemplified in the case of potassium benzoate [Eq.1].[15] The thermal effects induced by microwave-reactants interactions in this equilibrium were explored (Fig. 1).

$$PhCOO^-K^+ + n\text{-}Bu_4N^+Br^- \rightleftharpoons PhCOO^-n\text{-}Bu_4N^+ + K^+Br^- \quad [\text{Eq. 1}]$$

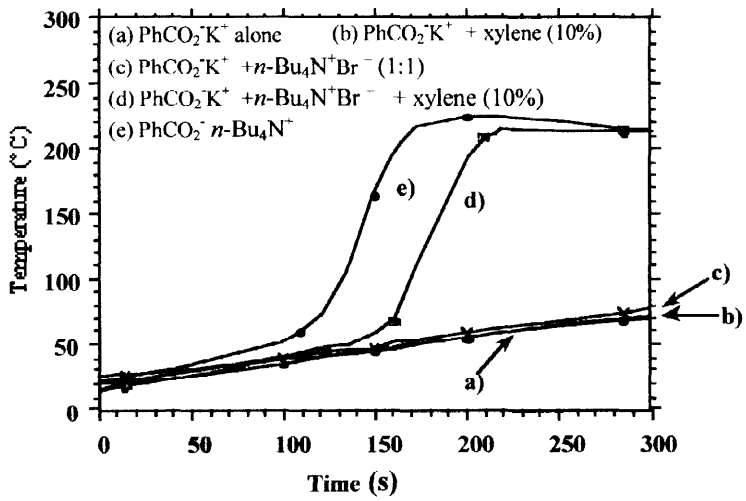


Fig. 1 : Thermal behavior induced by microwave irradiation of $PhCO_2K$ under different conditions (monomode reactor, 180W)

Even in the presence of TBAB (curve c), the temperature rise for solid potassium benzoate remains very modest. In the presence of small amounts of xylene (curve d), a non polar -i.e. inert *vs* irradiation-solvent, a large temperature rise provides evidence for the formation of tetrabutylammonium benzoate in the liquid phase, with the resultant positive thermal effect (curve d). The necessity for a liquid phase to promote ion-pair exchange between the two solids TBAB and $PhCOO^-K^+$ is therefore proven.

Hence, by coupling microwave technology and solvent-free solid-liquid PTC conditions, heating can result from the previous ion-pair exchange. We are therefore in possession of *a clean, selective and efficient methodology* to carry out organic reactions with substantial improvements in terms of reactions conditions and simplicity in operating procedures.[4] They are especially useful for poorly reactive systems involving for instance hindered electrophiles or long chain halides.[16]

4. Equipment [17,18] (Figure 2)

The most popular equipment is the domestic oven. The distribution of the electric field is non homogeneous (multimode system, a). Consequently, hot and cold spots coexist, making necessary a

preliminary mapping of the energy before use.[19] Nevertheless, a variety of organic syntheses can be effected with this simple, non expensive generator.

More sophisticated apparatus has to be used when accurate, reproducible results are required. The most reliable reactors have properly dimensioned waveguides leading to focusing (monomode system, b) with a subsequent homogeneous distribution in energy. They permit higher energy yields to be reached with lower power consumption, and can be used for products of limited stability. These generators are commercially available.[20]

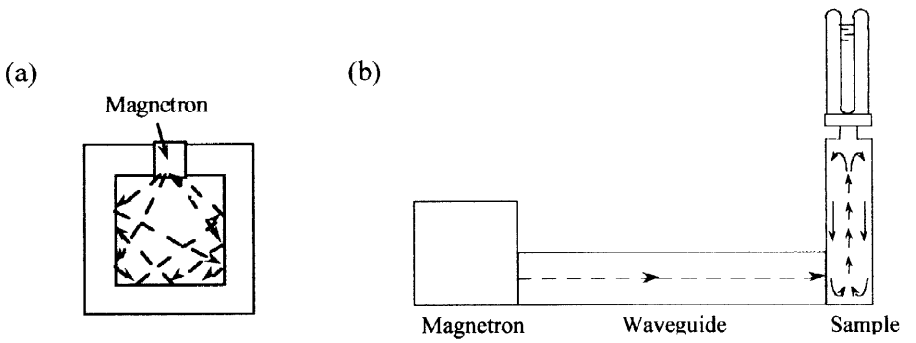


Fig. 2 : Dispersion of microwave energy : (a) in a domestic multimode oven ; (b) in a focused open vessel monomode reactor.

II- SYNTHETIC APPLICATIONS IN PHASE TRANSFER PROCESSES

Numerous reactions in organic synthesis can be achieved under solid-liquid PTC and microwave irradiation in the absence of solvent, generally under normal pressure in open vessels. Increased amounts of reactants can be concerned in order to ensure a better compatibility between the in-depth penetrability of materials and the radiation wavelength.

Since microwave activation is a rather recent technique, the number of examples can appear limited at the present time, but is rapidly expanding.

1. O-Alkylations

In conventional methods, PTC has provided interesting procedures for alkylation. Coupling with microwave activation has proved to be quite fruitful, as has already been illustrated in [Eq.1].

1.1. Esters Synthesis

1.1.1. Alkyl Acetates

Potassium acetate can be readily alkylated in a domestic oven using equivalent amounts of salt and alkylating agent in the presence of Aliquat 336 (10% mol.). Some main results, as exemplified for [Eq.2], are given in Table 1.[14,21]

$$CH_3COO^-K^+ + R\text{-}X \rightleftharpoons CH_3COOR + K^+X^- \qquad [\text{Eq. 2}]$$

Table 1 : Alkylation of $CH_3COO^-K^+$ under microwave (domestic oven, 600W)

RX	Time (min)	Final Temperature (°C)	**Yield** (%)
n-$C_8H_{17}Br$	1	187	98
n-$C_8H_{17}Cl$	1	162	98
n-$C_8H_{17}I$	2	165	92
n-$C_{16}H_{33}Br$	1	169	98

Yields are practically quantitative within 1-2 min. in all of the cases, regardless of the chain length, nature of the halide leaving group, and reagent amounts, at least within a range of 10 to 500 mmoles.

More recently, chinese authors have obtained similar results with *n*-butyl bromide using TBAB (10% mol.) and alumina (4:1/w:w) as the catalyst.[22] Benzyl acetate was also conveniently prepared from sodium acetate and a benzyl halide using microwave irradiation and PTC in synergy.[23]

1.1.2. Long Chain Esters

As a generalization of the above method, stearyl stearate was synthesized within 1 min. in a quantitative yield [Eq.3].[21]

$$C_{17}H_{35}COO^-K^+ + n\text{-}C_{18}H_{37}Br \xrightarrow[\text{MW (600 W) 1 min.}]{\text{Aliquat 10\%}} C_{17}H_{35}COOn\text{-}C_{18}H_{37} \quad (99\ \%) \qquad [\text{Eq. 3}]$$

1.1.3. Aromatic Esters

It is possible to perform the alkylation of aromatic acids directly without the necessity of preparing the reactive potassium salt in a discrete step, since it can be generated *in situ* by reacting the acid with a base (potassium carbonate or hydroxide) in the presence of a phase transfer catalyst.

$$ArCOOH + KOH \underset{}{\overset{\text{Aliquat 10\%}}{\rightleftharpoons}} ArCOO^-K^+ + H_2O \qquad [\text{Eq. 4}]$$

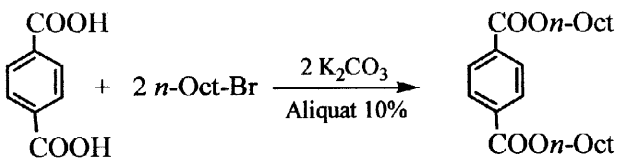
$$ArCOO^-K^+ + R\text{-}X \xrightarrow{\text{Aliquat 10\%}} ArCOOR + K^+X^- \qquad [\text{Eq. 5}]$$

An illustration of this principle is shown in [Eq. 4], whereby a volatile polar molecule is a by-product eliminated by microwave heating, and the equilibrium is shifted to completion. The second effect of irradiation is the activation of the alkylation step itself in [Eq.5]. All reagents can be used in the theoretical stoichiometry. Some indicative results are given in Table 2.[15]

Table 2 : Alkylation of potassium 4-Z-benzoate (domestic oven, 600W, 10% Aliquat)

		Yield (%)	
Z	Time (min)	Preformed salt	Salt *in situ*
H	2.5	99	99
NMe_2	3	97	100
OMe	2	82	98
CN	3	80	95
NO_2	2	81	95

A striking case in this series deals with terephthalic acid alkylation [Eq.6]. The specific effect of microwave irradiation appears clearly in this example, since, other factors being equal, the yields are unambiguously much higher.



[Eq. 6]

MW (600W)	7 min.	227°C	87%
Classical Heating	7 min.	227°C	20%

1. 2. Ether Synthesis

1.2.1. Aliphatic Ethers

Two types of conditions were studied for this reaction by Yuan *et al*, using either the alcohols or their corresponding halides as starting materials.[24,25] In the presence of quaternary ammonium salts, the reaction shown in [Eq.7] is completed within a few minutes. Typical results are given in Table 3.

$$ROH + R'X \xrightarrow{PhCH_2N^+Me_3Cl^-} R\text{-}O\text{-}R' + HX \qquad [\text{Eq. 7}]$$

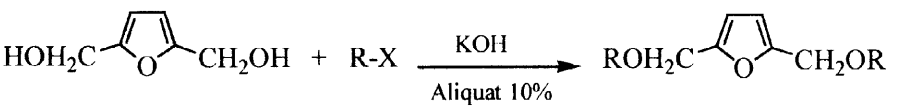
Table 3 : Synthesis of ethers in microwave oven (560W)

R	R'X	Time (min)	Yield (%)
Et	$PhCH_2Cl$	5	85
n-Bu	$PhCH_2Cl$	10	78
n-Oct	$PhCH_2Cl$	10	88
n-Oct	*n*-BuBr	10	78
$PhCH_2$	*n*-BuBr	10	92

This method was extensively applied to a wide range of Williamson syntheses in dry medium using K_2CO_3 + KOH as a base and NBu_4Br as the phase transfer agent and a variety of aliphatic alcohols (e. g. octanol and decanol, yields : 75-92%).[26]

1.2.2. Furanic Diethers [27]

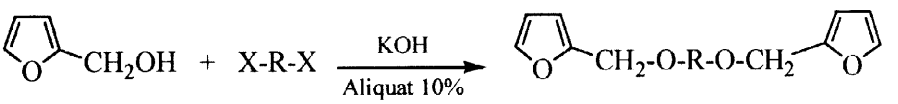
A new family of furanic diethers was obtained by alkylation of 2,5-furandimethanol [Eq.8] or furfuryl alcohol [Eq.9] (important derivatives from biomass) using microwave and PTC solvent-free conditions.



[Eq. 8]

Microwaves	Monomode Reactor (30W)	5 min.	180°C 93%
Conventional Heating (Oil Bath)		5 min.	180°C 41%

Diethers were synthesized with good yields and within short reaction times. When compared to classical heating, under otherwise comparable conditions, reactions times were improved by microwave activation. These optimized conditions were extrapolated to alkylation of furfuryl alcohol by dihalides [Eq.9].

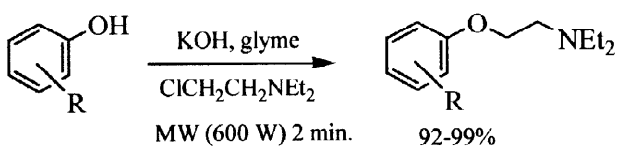


[Eq. 9]

Ex : X-R-X = $Br(CH_2)_{12}Br$ MW (60 W), 10 min., 170°C, 96%

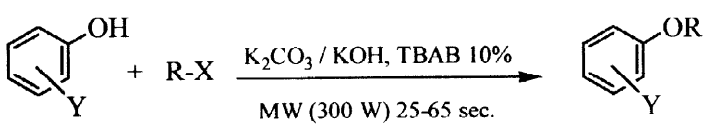
1.2.3. Phenolic Ethers

As compounds of biological interest, the preparation of gram quantities of aryl-2-(*N,N*-diethylamino)ethyl ethers was described in a conventional microwave oven using potassium hydroxide and glyme as the transfer agent, according to [Eq.10].[28]



[Eq. 10]

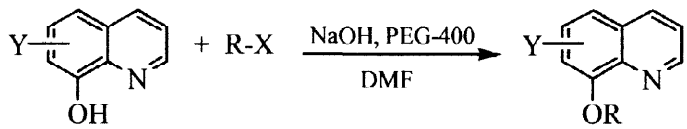
Under microwave irradiation, a number of phenols react remarkably fast in dry media with a number of primary alkyl halides to give aromatic ethers [Eq.11].[29]



[Eq. 11]

Ex : Y = H	R-X =	$PhCH_2Cl$	50 sec.	78%
		Me_2SO_4	25 sec.	87%
Y = *p*NH_2		$PhCH_2Cl$	40 sec.	89%

The syntheses of 8-quinolinyl ethers from 8-hydroxyquinolines and organic halides has also been recently reported under PTC conditions and microwaves [Eq.12].[30]

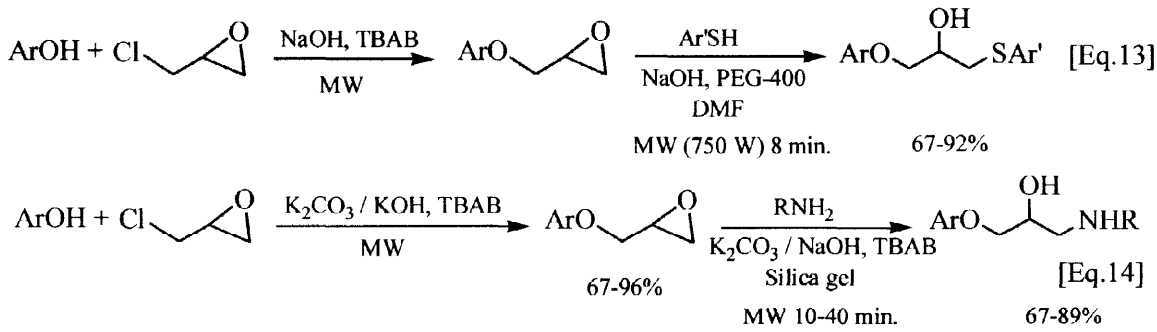


[Eq. 12]

MW (750 W) 3-15 min. 76-91%

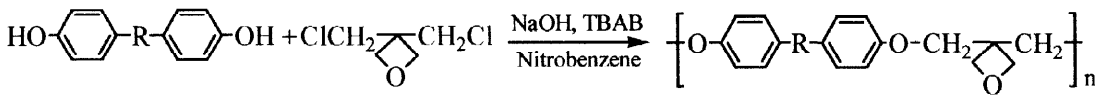
Ex : Y = H	R-X =	$PhCH_2Cl$	7 min.	87%
		$PhCOCH_2Br$	13 min.	91%

Alkylations of phenols with epichlorhydrin under PTC conditions and microwave irradiation were described twice in 1998. Subsequent ring opening of the epoxide group also performed using microwave [Eq.13][31] [Eq.14].[32] In the first case, a catalytic synthesis of chiral glycerol sulfide ethers was described,[31] while, in the second biologically active amino ethers were prepared.[32]



1.2.4. Phenolic Polyethers [33]

Polycondensations of 3,3-bis(chloromethyl)oxetane and various bisphenols were studied using the microwave-PTC technique [Eq.15].[31] The results obtained show the advantages of microwave fields in terms of the molecular weights for crystalline polymer as reflected in higher values of transition temperature Tg and melting points Tm and also in reactions times for all types of structures.



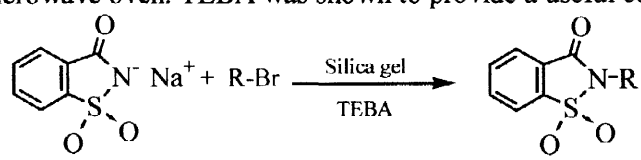
R = -N=N-, -S-, $-\overset{CH_3}{\underset{CH_3}{C}}-$, $-\overset{O}{C}-$ [Eq.15]

Ex : R = $-\overset{O}{C}-$		Microwave	Conventional Thermal
	Yield	72%	50%
	Tg	117°C	103°C
	Tm	256°C	232°C

2. N-Alkylations

2.1. Saccharin [34]

Rapid N-alkylation of saccharin [Eq.16] by a series of halides was performed on silica gel *via* its sodium salt in a microwave oven. TEBA was shown to provide a useful co-catalytic effect (Table 4).



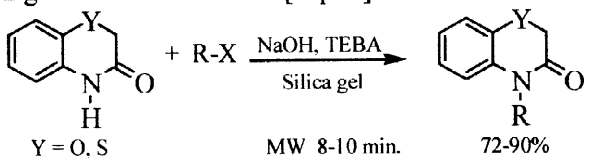
[Eq. 16]

Table 4 : N-Alkylation of saccharin under microwave (750 W)

R	Catalyst	Time (min)	Yield (%)
$PhCH_2$	None	4	8
	SiO_2	4	75
	SiO_2 + TEBA	4	92
n-$C_{16}H_{33}$	SiO_2	6	82
	SiO_2 + TEBA	6	97

2.2. Benzoxazinones and Benzothiazinones

Rapid N-alkylations of the title products were performed under PTC and microwaves[35] as well as Michael reactions[36] using the same conditions [Eq.17].



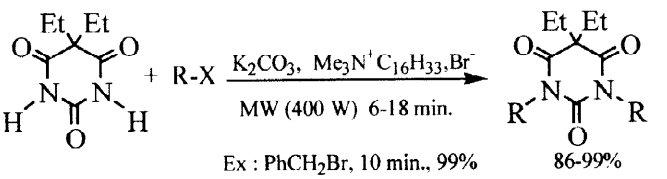
[Eq. 17]

Y = O, S MW 8-10 min. 72-90%

Ex : Y = O R-X = $PhCH_2Br$ 10 min. 84%

Y = S 10 min. 80%

2.3. Barbitone [Eq.18][37]

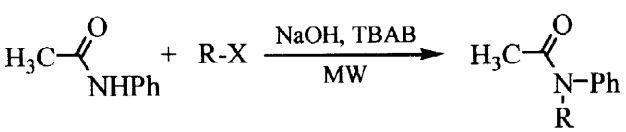


[Eq. 18]

Ex : $PhCH_2Br$, 10 min., 99% 86-99%

2.4. Acetanilide[38]

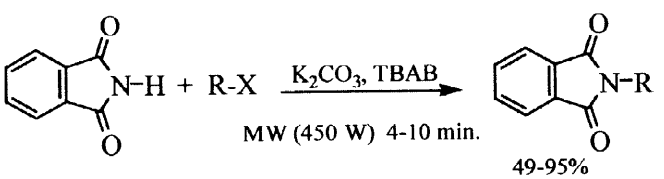
The N-alkylation of acetanilide under microwave irradiation in the presence of phase transfer catalyst has also been reported [Eq.19].



[Eq. 19]

Ex : R-X *n*-BuI 80 sec. 88%

2.5. Phthalimide : Gabriel reaction [Eq.20] [39]



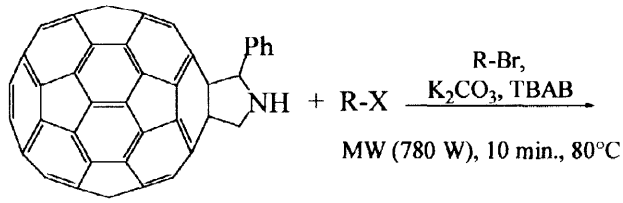
[Eq.20]

49-95%

Ex : R-X			
	$PhCH_2Cl$	4 min.	93%
	n-BuBr	4 min.	73%
	n-$C_{12}H_{25}I$	10 min.	95%

2.6. N-phenylpyrrolidino[60]fullerene[40]

A facile synthesis of a series of N-alkylpyrrolidino[60]fullerenes by PTC without solvent under microwave has been described [Eq.21].



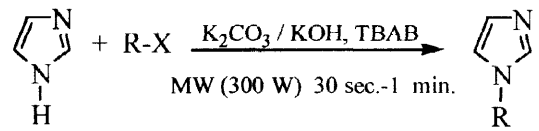
[Eq. 21]

Ex : R-X		
	$PhCH_2Br$	70%
	$CH_2=CH_2-CH_2Br$	39%
	n-$C_8H_{17}Br$	31%

The synergy between dry media and microwave irradiation was convincingly demonstrated in this work. For instance, in the case of allyl compound, the yield is only 16% after 24 hours in refluxing toluene, and no reaction occcurs after 10 min. at 100°C under classical heating, thus revealing an important specific microwave effect.

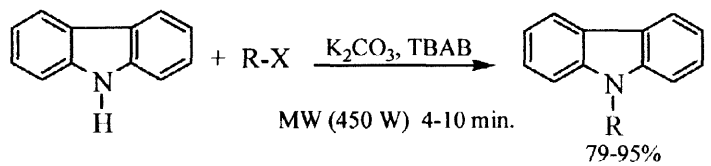
2.7. Azaheterocycles [41,42]

A number of azaheterocycles (i.e. pyrrole, imidazole, indole and carbazole) react remarkably fast with alkyl halides to give exclusively N-alkyl derivatives [Eq.22][41] [Eq.23].[42]



[Eq. 22]

Ex : $PhCH_2Cl$, 40 sec., 89% 73-89%

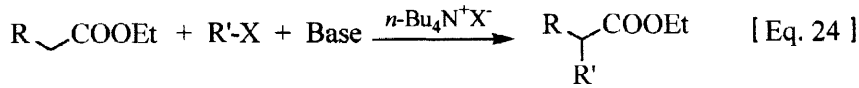


[Eq. 23]

Ex : R-X			
	$PhCH_2Cl$	4 min.	93%
	n-BuBr	4 min.	73%
	n-$C_{10}H_{21}Cl$	10 min.	95%

3. C-alkylation of Active Methylenes [43]

Several monoalkylations of functionalized acetates [Eq.24] have been described in a series of chinese papers using potassium carbonate either pure or mixed with potassium hydroxide. Significant results are given in Table 5.



[Eq. 24]

Table 5 : Mono-alkylation of functionalized acetates in microwave oven (650W)

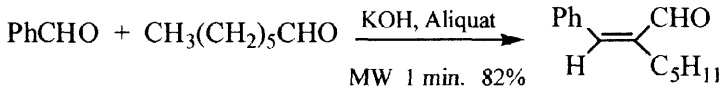
R	R'X	Time (min)	Yield (%)
$PhSO_2$ [44]	$PhCH_2Cl$	3	76
	n-BuBr	3	83
	n-OctBr	3	79
PhCH=N [45]	$PhCH_2Cl$	1	63
	n-BuBr	2	55
PhS [46,47]	$PhCH_2Cl$	4.5	83
	n-BuBr	4.5	59
CH_3CO [48]	$PhCH_2Cl$	3	81
	n-BuBr	4.5	61

Rapid monoalkylations are achieved in good yields when compared with classical ways. Of particular interest is the synthesis of α-amino acids via alkylation of aldimines under microwave activation. Subsequent acidic hydrolysis of the alkylated imine provides leucine, serine or phenylalanine in preparatively useful yields within 1-5 minutes.[45]

4. Nucleophilic Additions to Carbonyl compounds

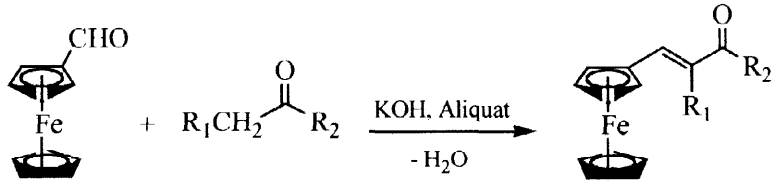
4.1. Aldol Condensation [49]

Jasminaldehyde was obtained classically from heptanal and benzaldehyde in 70% yield over 3 days at room temperature [Eq.25]. However, by using a 600 W domestic microwave oven, an enhanced yield of 82% was achieved within only 1 minute. The amount of side-products (self condensation of *n*-heptanal) decreased from 30 to 18% using this technique.



[Eq. 25]

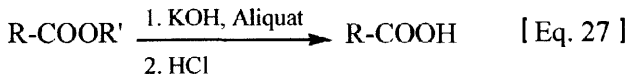
A second example of aldolization [Eq.26] is found in the « dry » reaction of ferrocene carbaldehyde with carbonyl compounds in the presence of potassium hydroxide and Aliquat as a catalyst.[50] Reactions which are too slow at room temperature are efficiently accelerated by microwaves, giving good yields within a few minutes.



[Eq. 26]

4.2. Ester Saponification [51]

Esters are easily saponified in a few minutes using powdered potassium hydroxide (2 mol. equiv.) and Aliquat (10% mol.) in the absence of solvent [Eq.27].



[Eq. 27]

Table 6 : Ester saponifications

		Multimode Oven (250W)		Monomode Reactor (90 W)			Classical Heating		
R	R'	Time (min)	Yield (%)	Time (min)	T (°C)	Yield (%)	Time (min)	T (°C)	Yield (%)
Ph	Me	0.5	87	1	205	96	1	205	90
Ph	*n*-Oct	1	83	2	210	94	2	210	72
2,4,6-$Me_3C_6H_2$	Me	2	75	2	140	84	2	140	38
2,4,6-$Me_3C_6H_2$	*n*-Oct	2	57	4	223	82	4	223	0

A few examples are summarized in Table 6, from which three important conclusions can be drawn :

i- Rapid and easy reactions occur, even with the most hindered mesitoic esters, which are otherwise practically non-saponifiable under classical conditions.[52]

ii- The advantage of using a monomode reactor versus a domestic oven appears clearly.

iii- More interesting from a fundamental viewpoint is the very strong specific non-thermal effect of microwave, as evidenced by comparison with classical heating. This effect grows as the ester reactivity falls.

4.3. Base Catalyzed Transesterifications [21]

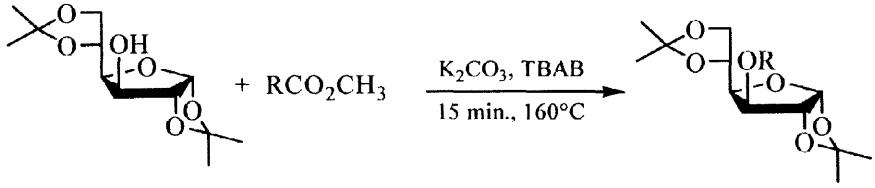
Transesterifications, such as that shown in [Eq.28], occur readily in microwave ovens due to the displacement of the equilibrium by evaporation of polar volatile methanol (Table 7).

$$ArCOOMe + n\text{-}C_8H_{17}OH \underset{\text{Aliquat}}{\overset{\text{Base}}{\rightleftharpoons}} ArCOOn\text{-}C_8H_{17} + MeOH \qquad [\text{Eq. 28}]$$

Table 7 : Base catalyzed transesterifications under microwave (600 W).

Ar	Base	Time (min)	Yield (%)
C_6H_5	KOH	3	40
	KO*t*-Bu	3	42
	K_2CO_3	2.5	90
2,4,6-$Me_3C_6H_2$	KOH	10	64
	KO*t*-Bu	10	68
	K_2CO_3	10	89

This study was next extended to the synthesis of benzoyl and dodecanoyl derivatives from protected carbohydrates.[53] Microwave assisted PTC transesterifications with methyl benzoate or dodecanoate were thus studied for several carbohydrates. Small amounts of dimethylformamide (DMF) were shown to be necessary to provide good yields (76-96%) with 15 minutes. Rate enhancements when compared to conventional heating (Δ) and specific microwave activation were especially noticeable when less reactive fatty compounds were involved [Eq.29].



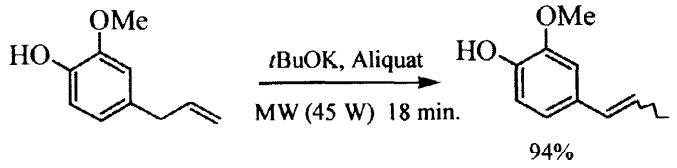
[Eq. 29]

R = Ph		MW	44%	
	DMF	MW	96%	Δ 21%
R = $CH_3(CH_2)_{10}$	DMF	MW	88%	Δ 0% (id. 12h)

5. Deprotonations

5.1. Base Catalyzed Isomerization of Allylic Aromatic Compounds [54]

Eugenol is a natural product available from a variety of essential oils (cinnamon-tree or piments leaves). Its isomerization [Eq.30] into isoeugenol, the starting material for synthetic vanillin, is rather difficult and proceeds in modest yields under relatively harsh conditions. It can be very efficiently prepared however using 2.2 molar equivalents of base and catalytic (5%) amounts of Aliquat in the absence of solvent.

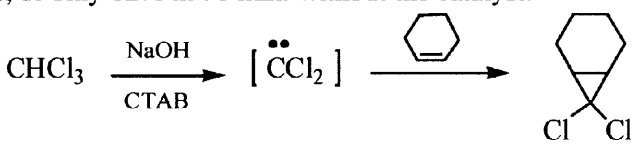


[Eq. 30]

5.2 Carbene Generation (α-elimination) [55]

Dichlorocarbene was generated under solid-liquid conditions using microwaves. Refluxing a mixture of $CHCl_3$, powdered NaOH and trace amounts of CTAB in cyclohexene under microwave

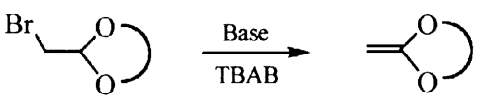
irradiation gave 90% of dichloronorcarane [Eq.31] within 20 min., versus 81% in 60 min. without microwave exposure, or only 12% in 90 min. without the catalyst.



[Eq. 31]

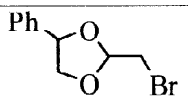
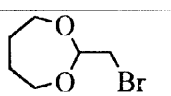
5.3. β-Elimination

Bromo acetals in basic media can lead to cyclic ketene acetals [Eq.32]. These β-eliminations, previously performed under solid-liquid PTC without solvent and with sonication,[56] were further improved by microwave irradiation (Table 8).[57]



[Eq. 32]

Table 8 : β-Eliminations on bromo acetals in a monomode reactor (75W). Comparison with sonochemical conditions and classical heating.

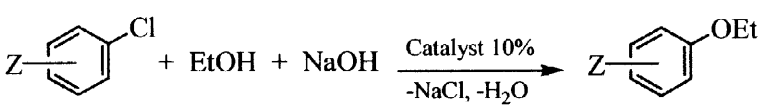
	Base	Ultrasound Conditions			Microwave Conditions			Classical Heating		
		t (h)	T (°C)	Yield (%)	t (min)	T (°C)	Yield (%)	t (min)	T (°C)	Yield (%)
	KOH, TBAB	1	75	81	10	130	81			
	t-BuOK, TBAB	1	35	70	5	75	87	5	75	36
	KOH, TBAB	1	75	81	10		28			
	t-BuOK, TBAB	1	45	70	5	60	95	5	64	41

With potassium *t*-butoxide and TBAB, higher yields are obtained faster than under sonication conditions or with conventional heating.

6. Miscellaneous Reactions

6.1. Nucleophilic Aromatic Substitution (S_NAr)

The irradiation of a mixture of *ortho* or *para*-nitrochlorobenzene and ethanol in the presence of sodium hydroxide and a phase transfer agent yields the corresponding ethoxy aromatic compounds within a few minutes [Eq.33].[58] The same procedure was subsequently applied to 2-chlorophenol.[59] In both cases, PEG 400 was shown to be the most efficient catalyst (Table 9).



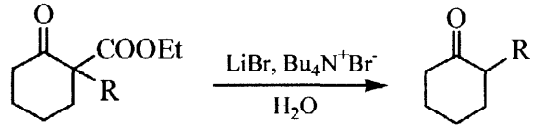
[Eq. 33]

Table 9 : Nucleophilic aromatic substitution under microwave (420-700W)

Z	Catalyst	Time (min)	Yield (%)
4-NO_2 [55]	none	2	14
	$PhCH_2N^+Me_3Cl^-$	2	51
	PEG 400	2	99
2-NO_2 [55]	PEG 400	2	99
2-OH [56]	$PhCH_2N^+Me_3Cl^-$	2	70
	PEG 400	2	82

6.2. Dealkoxycarbonylations of Activated Esters (Krapcho reaction)

This type of reaction is usually best performed in DMSO solution. A simpler procedure was proposed using anionic activation and microwave irradiation, with a metal salt as the reagent and a PTC in the absence of solvent.[60] This procedure was applied to the striking case of cyclic β-ketoesters and considerable improvements [Eq.34] (Table 10) can be noted when the maximum yields obtained under classical Krapcho conditions (< 20% when R≠H) are considered.[61]



[Eq. 34]

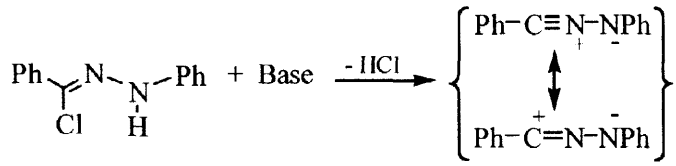
Table 10 : Dealkoxycarbonylation of cyclic β-ketoesters in a monomode reactor.

R	Microwave Conditions		T	Yield
	Time (min)	Power (W)	(° C)	(%)
H	8	30	138	96
Et	15	30	160	94
n-Bu	20	45	167	89
n-Hex	20	90	186	87

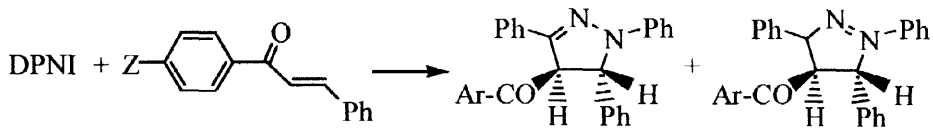
In order to verify the specific effects of microwave irradiation, the second experiment (R = Et) was performed using conventional oil bath heating under the same conditions of time and temperature (15 min., 160°C). No reaction was observed. Further heating for 3 hours led to total conversion but the yield (60%) was limited by product degradation. Clearly, when compared to conventional heating, microwave heating provides a large reduction in time, simplified experimental conditions, and the prevention of product degradation at high temperature.

6.3.[1,3]-Dipolar Cycloaddition of Diphenylnitrilimine [62]

Diphenylnitrilimine (DPNI) can be subjected to 1,3-dipolar cycloaddition with activated double bonds as dipolarophiles [Eq.35]. It can be generated *in situ* by reaction of hydrazonoyl chloride with a base.



DPNI [Eq. 35]



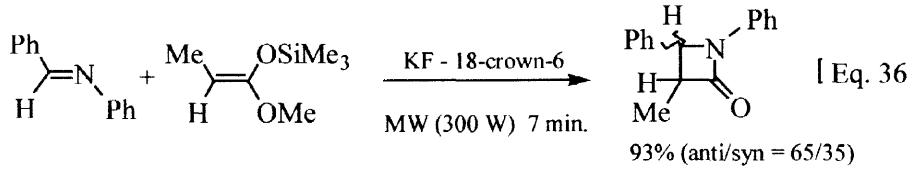
The cycloaddition can be performed almost quantitatively within 6 minutes under microwave irradiation using KF and Aliquat as a base. For the sake of illustration, results with substituted chalcones are indicated in Table 11. When the same reactions are performed all other factors being equal (time, temperature), no reaction occurs under classical thermal conditions. This behaviour once more confirms a specific radiation effect.

Table 11 : 1,3-dipolar cycloaddition of DPNI to chalcones in a monomode reactor (30 W)

Z	Time (min)	T. (°C)	Yield (%)
H	6	170	90
Br	5	170	93
Cl	6	174	95
Me	6	168	87
OMe	6	175	89

6.4. β-Lactams Synthesis [63]

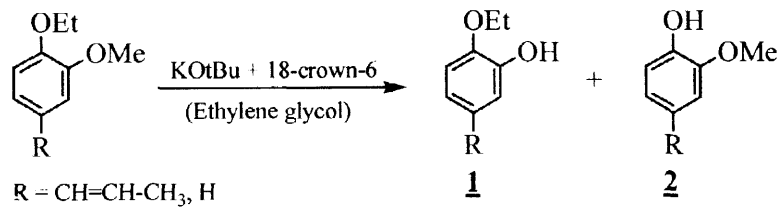
Silyl ketene acetals react with aldimines to give β-lactams using KF in the presence of a phase transfer agent (18-crown-6) within a few minutes using microwave irradiation in closed Teflon vessels [Eq.36].



[Eq. 36]

6.5. Selective Dealkylations of Aromatic Ethers [64]

Ethyl isoeugenol and ethoxy anisole can be selectively demethylated or deethylated using potassium *t*-butoxide in the presence of 18-crown-6 [Eq.37].



[Eq. 37]

Under solvent-free conditions only deethylation is observed whereas, in the presence of ethylene glycol (EG), the selectivity is totally reversed and demethylation becomes the major process. In both cases, considerable increases in reaction rate were observed under microwave irradiation when compared to classical heating (Δ) (Table 12) .

Table 12 : Selective dealkylations of ethoxy anisole (R=H)

		Time (min)	Temperature (°C)	Starting material (%)	1 (%)	2 (%)
-	MW	20	120	7	-	90
-	Δ	20	120	48	-	50
EG	MW	75	180	-	72	23
EG	Δ	75	180	98	-	-

III- CONCLUSION

The use of microwave irradiation to provide the activation energy for synthetic chemistry certainly leads to faster and cleaner reactions when compared to conventional heating. The coupling of microwave technology with solvent-free solid-liquid PTC conditions constitutes a new and particularly efficient, powerful, and attractive method.

Significant improvements in yields or reaction conditions can be achieved, together with considerable simplifications in operating procedures. The powerful synergistic combination of PTC and

microwave techniques has certainly allowed an ever increasing number of reactions to be carried out under clean and mild conditions. Furthermore, the inherent simplicity of the method can be allied with all the advantages of solvent-free procedures in terms of reactivity, selectivity, economy, safety and ease in manipulation.

Addendum

In the interim between submission and edition of this report, several interesting publications in the field appeared. They concern essentially :

- the alkylation and arylation of pyrazoles[65] as an interesting one-pot synthesis of 1-heteroarylpyrazoles;
- the alkylation of 2-methoxyphenol with 1,2-dibromoethane followed by reaction with potassium phthalimide to give 2-(2-methoxyphenoxy)ethylamine[66];
- the synthesis and isomerization of octylthiocyanate[67,68] by reacting *n*-octyl bromide with KCN in the presence of TBAB and subsequent isomerization to isothiocyanate;
- the methylation of 3,4-dihydroxybenzaldehyde [67,68] by methylene iodide in the presence of TBAB on carbonate surface;
- the reductive decyanation of alkyldiphenylmethanes in aqueous sodium hydroxide and PEG-400.[69]

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André Loupy

Jean-Louis Luche

Alain Petit

Sandrine Deshayes received her PhD in 1995 from the Orsay University under the direction of Prof. M. Momenteau in the field of synthesis of hemoprotein models. After working for Rhône Poulenc Rorer as postdoctoral position, she conducted a new study in Dr. A. Loupy's group in Orsay on the synthesis under microwave activation applied to Diels-Alder reactions from 1997 to 1998.

Marion Liagre was born in 1974. She received her diploma (DEA in organic chemistry) in 1996 from Université Paris-Sud (Orsay). She is currently carrying out her doctoral work under the supervision of Dr. A. Loupy on the regioselective synthesis of azolic fungicides under microwave irradiation without base or solvent.

André Loupy, director of research, received his PhD in 1975 from the University of Paris-South under the direction of Dr. J. Seyden-Penne in the Centre National de la Recherche Scientifique in Thiais. His current research interests focus on medium effects in organic synthesis including solvent and salt effects, solvent-free conditions in synthesis with special interest for supported reactions, phase-transfer catalysis, and since 1987 with microwave activation especially when coupled to solvent-free procedures. Together with Prof. J. Hamelin, he was the recipient of the M.J. Collins Award in 1998 for creative work in microwave chemistry.

Jean-Louis Luche received his diploma from Ecole Nationale Supérieure de Chimie in 1963, and his PhD in 1968 from Université de Paris, under the direction of Prof. H. Kagan, on the stereochemistry of monocyclic beta-lactams. After a post-doctoral stay in London (Canada) where he studied the flash thermolysis technique with Prof. P. de Mayo, he moved to Grenoble, where he started a study of the uses of lanthanides in organic chemistry (e.g. cerium chloride-sodium borohydride). In 1980, he published the first paper describing a synthetic application of ultrasound for organic synthesis (the sonochemical Barbier reaction), thus launching what is now known as "sonochemistry". Now in the Université de Savoie in the group of Prof. C. Petrier, he develops his research around the question "sonochemistry and green chemistry: a common future ?"

Alain Petit was born in 1950 near Paris. He received his diploma of Engineering in Industrial Chemistry in 1986 from CNAM in Paris. In 1973, he obtained a position in CNRS in the Physical Chemistry Laboratory in Orsay (direction : Mrs. A. Bernas). In 1983, he integrated to the "Laboratoire des Réactions Sélectives sur Supports" (direction : Prof. G. Bram then Dr. A. Loupy). His current interest is focused on the development of solvent-free procedures in organic synthesis involving phase transfer catalysis and supported reagents coupled with microwave activation.