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Application of Microwave Irradiation to Phase-Transfer Catalyzed Reactions

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Abstract:

By coupling microwave activation and PTC conditions, substantial improvements in numerous organic reactions are described under simple and safe conditions. Generally, better yields are obtained under faster and cleaner reactions when compared to those from conventional heating. Very often, solvent can be avoided during the reaction when the electrophile is a liquid and can therefore act both as a reagent and the organic phase, leading to efficient green chemistry procedures.

Introduction

Microwave irradiation is a rapid way of heating materials for domestic, industrial and medical purposes. Recently, microwave techniques have become a widely accepted and increasingly popular technology in organic chemistry as an alternative to, and often improvement for, conventional heating.[1] Microwaves offer a number of advantages over conventional heating such as noncontact heating (reduction of over-heating of material surfaces), energy transfer instead of heat transfer (penetrative radiation), material-selective and volumetric heating, fast start-up and stopping, and last, but not least, a reverse gradient as heat starts to build up from the interior (core) of the material body.[2] Heating in microwave cavities is based upon the ability of some polar liquids and solids to absorb and transform electromagnetic energy into heat. In order to support the above statement, it is clearly evident from the annual number of publications that microwave-assisted chemistry is growing rapidly with more than 3000 publications by the middle of 2008 since the pioneering works of Gedye[3] and Giguere[4] in 1986 (Figure 1).

The range of microwave frequencies occupies the electromagnetic spectrum between radio frequencies and infrared radiation with frequencies from 300 GHz to 300 MHz, which correspond to wavelengths of 1 cm to 1 m, respectively. The major applications fall into two categories, depending on whether they are used for transmission of information (telecommunication) or transmission of energy. However, the extensive application of microwaves in the field of telecommunication (e.g., most of the wavelengths in the range of 1−25 cm are used for mobile phones, radar, and radar line transmissions) has caused only specially assigned frequencies to be allocated for energy transmission (i.e. for industrial, scientific or medical applications). Currently, to minimize interferences with telecommunication devices, these household and industrial microwave applicators are operated only at a few precise frequencies with narrow tolerances that are allocated under international regulations. For example, the most common microwave applicators (i.e. domestic microwave ovens) use 2.45 GHz. This is probably why most commercially available microwave reactors devoted for chemical use operate at the same frequency; however, some other frequencies are also available.[5]

Microwaves and Phase-Transfer Catalysis. In chemical syntheses under the action of microwave irradiation, the most successful applications are found in the field of solvent-free procedures.[6] In these systems, microwaves interact directly with the reagents and can, therefore, drive chemical reactions more efficiently. The possible acceleration of such reactions might be optimum, because they are not moderated or impeded by solvents. Reactions on solid mineral supports, and, in turn, the interaction of microwaves with the reagents on the solid-phase boundary, which can substantially increase the rate of the reactions, are of particular interest as the supports are strongly and homogeneously heated under microwave irradiation, whereas heating is not efficient by classical heating as they behave as poor conducting species.[7]

Phase-transfer catalysis (PTC) reactions are perfectly tailored for microwave activation, and the combination of solid−liquid PTC and microwave irradiation gives the best results in this area:[8]

(1) after ion pair exchange with the catalyst, the nucleophilic ion pair $[Q^+Nu^-]$ is a highly polar species especially prone to interaction with microwaves;

(2) the extraction processes during the reaction, in which a PTC mechanism is mainly involved, can be accelerated on the

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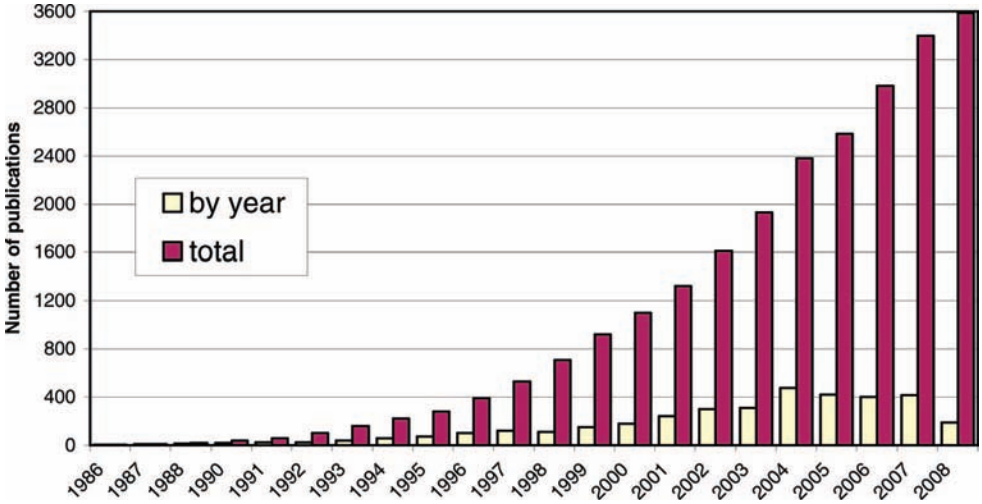

Figure 1. **Number of publications on microwave-assisted synthesis for the period 1986−2008.**

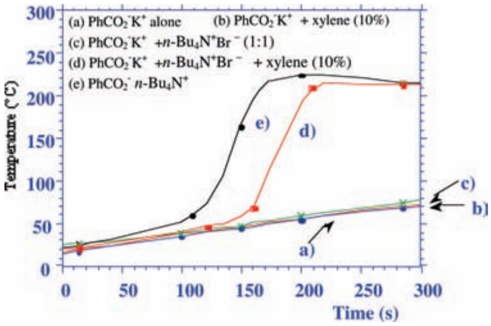

Figure 2. **Thermal behavior induced by microwave irradiation of $PhCO_2K$ under different conditions (monomode reactor, 180 W).**[9]

phase boundary, and an increase of reaction rate might be expected; and

(3) reactions under solid−liquid PTC, like reactions on mineral supports under solvent-free conditions, often suffer from difficulties with heat transfer through the reaction medium and homogeneous heating under conventional conditions. Because microwave irradiation is a means of volumetric heating of materials, temperature is more uniform under microwave conditions. Improvement of temperature homogeneity and heating rates implies faster reactions and less degradation of the final products.

Similarly to classical PTC reaction conditions, the role of catalyst is very important for microwave-assisted solid−liquid PTC conditions. It has been found that in the absence of a catalyst, the reactions proceed very slowly or not at all. The need to use a phase-transfer catalyst implies also the application of at least one liquid component, whether the electrophilic reagent or the solvent. Ion-pair exchange between the catalyst and nucleophilic anions proceeds efficiently only in the presence of a liquid phase.[9] During the investigation of the formation of tetrabutylammonium benzoate from potassium benzoate and tetrabutylammonium bromide, potassium benzoate did not absorb microwaves significantly (Figure 2, curves a and b). Even in the presence of tetrabutylammonium bromide (TBAB), the temperature increase for solid potassium benzoate was very modest (Figure 2, curve c). After addition of small amounts of xylene (Figure 2, curve d), a nonpolar solvent (i.e. inert to microwave irradiation), a large temperature increase provides evidence for the formation of tetrabutylammonium benzoate in the liquid phase, from which the positive thermal effect results (Figure 2, curve e).

It must be stressed that a liquid component can be substituted with an efficient absorber of microwave irradiation together with a low-melting component. The use of most typical PTC solvents (nonpolar aromatic or aliphatic hydrocarbons, or highly chlorinated hydrocarbons) are most interesting for microwave activation, because such solvents are transparent or absorb microwaves only weakly. They can, therefore, enable specific absorption of microwave irradiation by the reagents, and the results or product distributions might be different under microwave and conventional conditions.[7] This is essentially useful for poorly reactive systems involving, for instance, hindered electrophiles or long chain halides.

Numerous reactions in organic synthesis can be achieved under solid−liquid PTC and with microwave irradiation in the absence of solvent, generally under atmospheric pressure in open vessels. Increased amounts of reactants can be used to ensure better compatibility between the in-depth penetrability of the radiation wavelength of 12.2 cm (2.45 GHz), the optimal point for convenient and accurate wave absorption.

In general, applying PTC conditions, it is hard to avoid the use of solvents. Even though, a reaction is running under solid−liquid PTC conditions, a solvent has to be use to separate organic materials from inorganic salts. However, applying solid−liquid PTC under microwave conditions and then a solvent for extraction, there are still a number of advantages when comparing to conventional PTC reaction at the presence of a solvent. First, applying microwave irradiation under solid−liquid conditions, one needs to bring to the proper reaction temperature less material, which means that much less energy is needed to carry out such a process. Second, under solid−liquid conditions, one is not limited by the boiling point of a solvent, and it is often possible to heat the reaction mixture to significantly higher temperatures than boiling points of most common organic solvents and, therefore, accelerate a reaction (microwave effect). Moreover, due to less dilution of the

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Table 1. **Synthesis of *n*-octyl acetate under microwave and PTC conditions (5 min, 160°C).**[17]

microwave reactor	amounts of materials [g (mol)] CH_3COOK	*n*-OctBr	Aliquat	total amount (g)	yield (%)
Synthewave 402	4.9 (0.05)	9.7 (0.05)	1 (0.0025)	15.6	98
Synthewave 1000	196 (2)	386 (2)	40.4 (0.1)	622.4	98

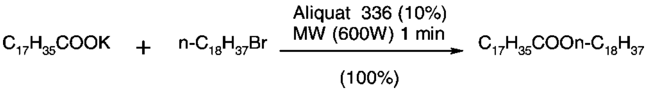
substrates in the absence of solvent during the reaction, it is possible to observe their enhanced reactivity. Third, at the extraction stage, one can apply low boiling solvents, which in turn simplifies the workup procedure comparing to problems with removing high-boiling solvents. Eventually, running a reaction without solvents, one can reduce volumes of reaction vessels, which requires less space needed for an apparatus. As it has been shown, microwaves work perfectly well under solid−liquid PTC systems, in which there are difficulties to provide energy under conventional heating conditions. However, in some cases, under microwave irradiation and solid−liquid PTC systems, stirring is need to provide more uniform reaction conditions. The effect of agitation under microwave conditions is discussed in the next paragraphs.

Synthetic Application of Microwaves in PTC Reactions. Phase-transfer catalysis (PTC) is one of the most useful techniques when anionic activation is concerned. It has been applied to over 600 industrial processes in a variety of industries such as intermediates, dyestuffs, agrochemicals, perfumes, flavours, pharmaceuticals and polymers. It is worth remarking that the sales of products made by use of PTC catalysis exceeds \$12 billion (USD) per year.[10–13] However, the effluent-treatment problem associated with soluble PTC, requiring a large quantity of water to wash the organic phase, has hampered exploitation of PTC in many other bulk industries. Thus, the applications of PTC are practically confined to the synthesis of low-volume and high-cost specialty, agro and pharmaceutical chemicals.[14] The reactions in which PTC catalysis has been successful include such important chemical transformations as C-, N-, O- and S-alkylations, etherification, esterification, transesterification, condensation, carbene reactions, nucleophilic displacements, oxidation, epoxidation, and polymerization. Therefore, it should be stressed that in this contribution it is not our intention to review a great number of papers reporting the use of PTC catalysis under microwave irradiation in industrially important reactions, but rather to give representative examples to demonstrate the scope and usefulness of these reactions.

O-Alkylations. In conventional methods, PTC has provided interesting procedures for O-alkylation, and coupling PTC conditions with microwave activation has proved to be quite effective for such reactions.

Aliphatic Esters. Potassium acetate can be readily alkylated in a microwave oven by use of equivalent amounts of salt and alkylating agent in the presence of Aliquat 336 (10 mol %).Yields are always almost quantitative within 1−2 min, irrespective of chain length and the nature of the halide leaving groups.[15,16] These procedures were scaled up from 50 mmol to the 2 mol scale (i.e. from 15.6 to 622.4 g of total starting materials) in a larger batch reactor.[17] Yields were equivalent to those obtained under similar conditions (5 min, 160 °C) in laboratory-scale experiment (Table 1).

Scheme 1



$$C_{17}H_{35}COOK + n\text{-}C_{18}H_{37}Br \xrightarrow[(100\%)]{\text{Aliquat 336 (10\%) MW (600W) 1 min}} C_{17}H_{35}COOn\text{-}C_{18}H_{37}$$

As a generalization of the above method, stearyl stearate was synthesized within 1 min in a quantitative yield (Scheme 1).[16] Moreover, it has been shown that reaction of carboxylic acids with benzyl halides, which does not occur when heated conventionally, could be performed efficiently under the action of microwave irradiation in the presence of a quaternary ammonium salt as a catalyst.[18]

In turn, applying microwave irradiation, Mariani et al. described the synthesis of some aliphatic esters useful as cosmetic ingredients; for example, 2-ethylhexyl pivalate, isopropyl myristate, butyl palmitate, and dibutyl sebacate under PTC conditions.[19]

Aromatic Esters. It is possible to alkylate benzoic acids directly, without the need to prepare reactive potassium salts in a separate previous step, because they can be generated in situ by reacting the acid with a base (potassium carbonate or hydroxide) in the presence of a phase-transfer catalyst. A volatile polar molecule (such as water in the case of RCOOH + KOH), which is a byproduct, is eliminated as a result of the microwave heating, and the equilibrium is shifted to completion. The second effect of irradiation is the activation of the alkylation step itself; thus, all the reagents can be used in the theoretical stoichiometry.[9,20] Furthermore, solid−liquid solvent-free PTC was applied, with noticeable improvement and simplification over classical procedures in a green chemistry context, to the synthesis of some aromatic esters useful as cosmetic ingredients; for example, 3-methylbutyl-4-methoxycinnamate, 2-ethylhexyl-4-methoxycinnamate, 2-ethylhexyl 4-(dimethylamino)benzoate and

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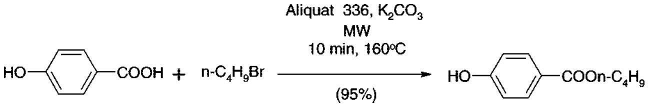
Scheme 2



Scheme 3

$$\text{R-OH} + \text{R'-X} \xrightarrow[\text{(45-91\%)}]{\text{TBAB, KOH, K}_2\text{CO}_3\ \ \text{MW}\ \ 98\text{-}175\,^\circ\text{C, 45-100 s}} \text{R-O-R'}$$

TBAB: tetrabutylammonium bromide
R = n-Dec, n-Oct, n-Bu; R' = Bzl, n-Hex, n-Oct, allyl

2-ethylhexyl salicylate, well-known ultraviolet B sunscreen filters; 4-isopropylbenzyl salicylate, UV absorber and cutaneous anti-lipoperoxidant; propyl 4-hydroxybenzoate and butyl 4-hydroxybenzoate (Parabens), antimicrobial agents (Scheme 2).[21]

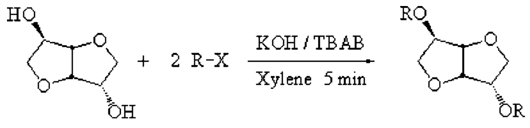
O-Alkylation reactions of carboxylic acids such as aryloxyacetic acids (unsubstituted furoic acids and benzofuroic acids) with (un)substituted ω-haloacetophenones in dry media under microwave and PTC conditions were also described.[22]

Aliphatic Ethers. The synthesis of aliphatic ethers under microwave irradiation using either the alcohols or corresponding halides as starting materials was studied by Yuan et al.[23] In the presence of quaternary ammonium salts, the reactions were completed within a few minutes with yields in the range of 78−92%. This method has been extensively applied to a wide range of Williamson synthesis in dry media with potassium carbonate and potassium hydroxide as bases, tetrabutylammonium bromide (TBAB) as a phase-transfer agent, and a variety of aliphatic alcohols (e.g, *n*-octanol and *n*-decanol, giving yields of 75−92%) under microwave irradiation (Scheme 3).[24]

A new family of furanic diethers were obtained by alkylation of 2,5-furandimethanol under the action of microwaves and PTC solvent-free conditions.[25] The diethers were synthesized in high yields (~90%) within short reaction times (5 min). When compared with classical heating, under otherwise comparable conditions, reaction times were noticeably reduced in the case of microwave activation. Also, the direct O-alkylation of 2-bromo-3-pyridinol via the standard Williamson reaction led to competitive reactions owing to the drastic experimental conditions required (basic medium, high temperatures, long reaction times). Very short reactions times of 45−60 s proved to be sufficient to achieve O-alkylation almost quantitatively under microwave irradiation.[26]

Within the frame of valorization of nonalimentary agricultural products and green chemistry context, a series of new ethers has been obtained by alkylation of dianhydrohexitols (i.e., isosorbide, isomannide, isoiodide) under the action of microwave irradiation and PTC conditions (Scheme 4).[27] Yields exceeded 90%, a dramatic improvement compared with those from conventional heating, despite similar temperature profiles. The best yields, for example from isosorbide, were obtained in the presence of a small amount of xylene and TBAB as catalyst at 140 °C (Table 2).

Scheme 4



R = *n*-Oct, ArCH_2, $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2$
X = Cl, Br

Later a number of polyethers were synthesized from isosorbide and isoidide by means of a microwave-assisted PTC method,[28] which is discussed below.

Aromatic Ethers. Under the action of microwave irradiation, several phenols react remarkably fast in dry media with primary alkyl halides to give aromatic ethers.[29] Lately, an extensive kinetic study of the alkylation of phenol, effects of catalyst and reagent concentrations, agitation, volume and temperature that revealed a synergetic effect between PTC and microwave irradiation was published.[30]

Aryl-2-(*N,N*-diethylamino)ethyl ethers, compounds of biological interest, were prepared in gram quantities with potassium hydroxide and glyme as the transfer agent.[31] 2′-Benzyloxyacetophenone, an important intermediate for the manufacture of drugs, was obtained by a synergistic combination of solid−liquid PTC and microwave irradiation.[32] The rates of reaction are increased by orders of magnitude and the reaction is selective at 80 °C, in comparison with liquid−liquid PTC which is slow and produces byproduct. In turn, catechol was reacted with β-methallyl chloride under the action of microwaves and PTC conditions; yields of 2-methallyloxyphenols varied from 59 to 68% under liquid−liquid conditions, whereas no reaction was observed in a solid−liquid PTC procedure.[33] In order to improve the synthesis of potential cosmetic compounds, alkylation of mono- and dihydroxybenzaldehydes with long-chain halides was efficiently realized under solvent-free microwave and PTC conditions.[34] In the presence of Aliquat 336, the reactions were completed within 15 min with 96% yield. The alkylations of 8-hydroxyquinolines as well as 7-hydroxy-4-methyl coumarin

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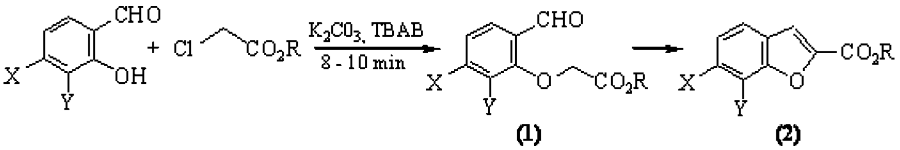
Table 2. **Reaction of isosorbide with several alkylating agents in the presence of potassium hydroxide and tetrabutylammonium bromide (TBAB) (relative amount 1:3:3:0.1) under microwave irradiation in a xylene solution.**[27]

R−X	time (min)	temperature (°C)	yield (%) MW[a]	Δ[b]
n-$C_8H_{17}Br$	5	140	96	10
$C_6H_5CH_2Cl$	5	125	98	13
3-Cl-$C_6H_4CH_2Cl$	5	125	95	15
4-Cl-$C_6H_4CH_2Cl$	5	125	96	14
3-F-$C_6H_4CH_2Cl$	5	125	95	15
$CH_3CH_2OCH_2CH_2Br$	30	100	78	45

[a] MW - microwave irradiation. [b] Δ - conventional heating under similar conditions and temperature profiles.

Scheme 5



with desyl chloride were also presented.[35,36] The reactions were carried out for 2−13 min with reaction yields ∼90%.

Alkylations of phenols and thiophenols with epichlorhydrin under PTC conditions resulted in glycidyl ethers, and subsequently, ring-opening reactions of the oxirane ring were also performed under microwave irradiation.[37,38] Thus, biologically active amino ethers and chiral glycerol sulfide ethers were prepared. Recently, an extensive investigation on the alkylation of phenol with epichlorhydrin, the effect of base and nature and position of substituents, effects according to reaction mechanism, was published.[39] It is worth stressing that the results obtained under microwave irradiation were much better than those derived from classical methods described in the literature, concerning selectivity, conversion and yield of suitable product.

Finally, it was shown that condensation of salicylaldehyde and its derivatives with a variety of esters of chloroacetic acids in the presence of TBAB led to the synthesis of benzo[*b*]furans by means of a solid−liquid PTC reaction under microwave irradiation (Scheme 5).[40]

The mixture of aldehydes and chloroacetic acid esters were adsorbed on potassium carbonate and then irradiated in an open vessel for 8−10 min to afford benzo[*b*]furans 65−96% yield. Recently, this reaction was studied with a thermovision camera, which showed that high temperature gradients can be generated during the reaction under microwave irradiation (Figure 3).

It was found that a high-temperature gradient within the reaction mixture generated by microwaves leads to a higher conversion of reactants or/and reaction rates, which in turn might be a reasonable explanation to the so-called nonthermal microwave effects, i.e., an increase of reaction rates that is inadequate to the temperature of reaction medium. Table 3 shows the influence of the experiment conditions, i.e. rotation and/or agitation of the reaction mixture on average reaction selectivity.[41]

The mechanical stirring with a quartz spatula placed within the reaction mixture improved the thermal homogeneity of the reaction mixture to greater extend than the rotation of the reaction vessels (Table 3, entry 3), the results are comparable to those obtained under conventional conditions. It was also shown that addition of an interliquid, *n*-decane, (Table 3, entry 4), which was added in such an amount that formed a 1−2 mm layer over the top of the reaction mixture, improved temperature homogeneity too; however, it was a bit difficult to observe it with the thermovision camera and visually, but the fiber-optic thermometer showed the same temperature (i.e., ∼110 °C) at every region of the reaction mixture. The results presented above are important because one can expect that the overall reaction yields given in Table 3 should be similar for all the experiments and do not show significant differences during additional rotation of the vessels and/or stirring of the reaction mixtures. It can be assumed that overall energy input given by microwaves is similar in all the cases; thus, the reaction rates can be different in different regions of the reaction mixture because the temperatures are different, but the overall reaction rates should be comparable. In fact, we observed the opposite

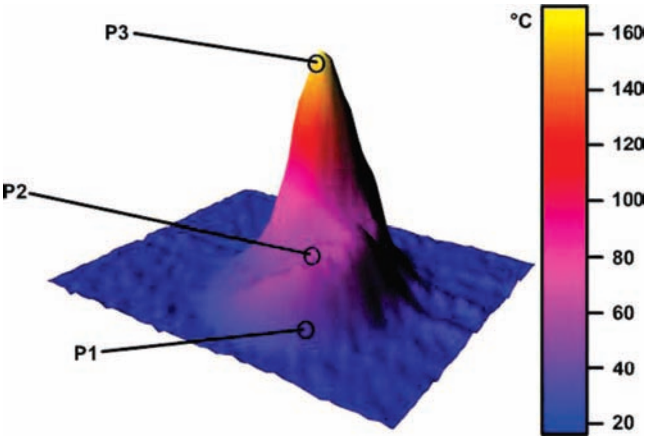


Figure 3. **Thermovision photograph of the surface of the reaction mixture of salicylaldehydes and chloroacetic acid esters on potassium carbonate support.**[41]

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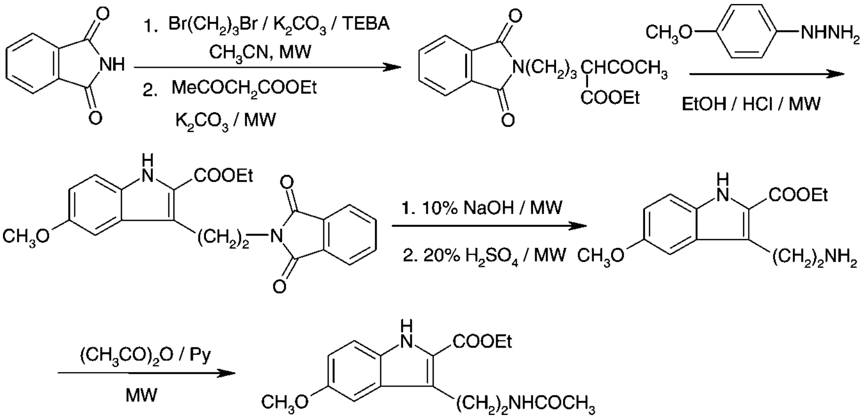
Table 3. **Influence of the experimental conditions, i.e. rotation and/or agitation of reaction mixture on average[a] reaction selectivity.**[41]

no	selectivity (Scheme 5)[a], [%] **1**	**2**	description
1	33	67	no stirring
2	70	30	vessel rotation
3	84	16	vessel rotation and stirring
4	100	0	no stirring, addition of 6 mL of decane
5	67	33	no stirring, vessel rotation
6	77	23	no stirring, vessel rotation

[a] Average selectivity determined by GC/MS from entire reaction mixture. All the microwave experiments were carried out under the same conditions: maximal microwave power 240 W, maximal temperature 110 °C.

Scheme 6



situation; the increase in temperature homogeneity caused a decrease of the overall reaction yields and made them comparable to those obtained under conventional conditions.

Thus, before considering the increase of reaction rates by special microwave effects (thermal or nonthermal), first we need to consider all the factors that might influence chemical reactions under microwave conditions such as reaction mechanism, temperature profiles (gradients), and in particular, proper design of the experiment (i.e. the same reaction conditions under microwave and conventional conditions as well as correct temperature measurement).[41]

N-Alkylations. Rapid N-alkylation of saccharin by a series of halides was performed inside a microwave oven within 4−6 min on silica gel via its sodium salt. Phase-transfer catalyst, TEBA, was shown to provide a useful cocatalytic effect to afford the products with 92−97% yield.[42] Later, in a similar manner, N-alkylation of benzoxazinones and benzothiazinones was performed under PTC conditions and microwave irradiation.[43] 5,5-Diethylbarbituric acid was also *N*,*N*-dialkylated in a good yield in the presence of a lipophilic ammonium salts and potassium carbonate when reaction mixtures were irradiated in a microwave oven to give the product with 99% yield within 10 min.[44]

N-Substituted amides and lactams can be rapidly N-alkylated under solid−liquid PTC conditions by use of microwave irradiation. The reactions were performed simply by mixing an amide with 50% excess of an alkyl halide and a catalytic amount of TBAB. These mixtures were adsorbed on a mixture of potassium carbonate and potassium hydroxide[45] and then irradiated in an open vessel in a microwave oven for 55−150 s. The starting reagents in Gabriel amine synthesis, *N*-alkylphthalimides, were obtained under the action of microwave irradiation in a solid−liquid PTC system. The reactions were conducted with high yield (50−90%) simply by mixing of phthalimide with 50% excess alkyl halide and catalytic TBAB, which were later adsorbed on potassium carbonate. Irradiation of the reaction mixtures in a microwave oven led to the desired phthalimide derivatives within a short time (4−10 min).[46] Finally, melatonin was prepared from phthalimide by N- and C-alkylation, cyclization, hydrolytic decarboxylation and acetylation. The four-pot reactions were carried out under microwave irradiation in good yields within short reaction times (Scheme 6).[47]

In turn, *N*-ethylaniline was alkylated by reaction with benzyl chloride under liquid−liquid PTC conditions in the presence of 30% sodium hydroxide solution and cetyltrimethylammonium bromide (CTAB) as a catalyst. Microwave irradiation (25 min) of the reaction mixture in a sealed vessel afforded *N*-benzyl-*N*-ethylaniline in 90% yield, compared with the yield from 16 h of conventional heating (oil bath).[48]

Under microwave irradiation several azoheterocycles (i.e. pyrrole, imidazole, indole and carbazole) can react fast with

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Scheme 7

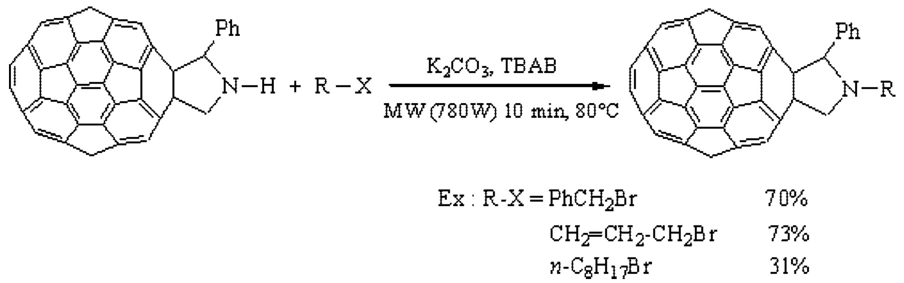


Table 4. **Monoalkylation of functionalized acetates in a microwave oven (Scheme *8*) (650 W).**

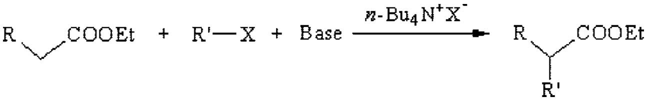
R	R′X	time (min)	yield (%)	lit.
$PhSO_2$	$PhCH_2Cl$	3	76	
	n-BuBr	3	83	53
	n-OctBr	3	79	
PhCH=N	$PhCH_2Cl$	1	63	54
	n-BuBr	2	55	
PhS	$PhCH_2Cl$	4.5	83	55, 56
	n-BuBr	4.5	59	
CH_3CO	$PhCH_2Cl$	3	81	57
	n-BuBr	4.5	61	
COOEt	$PhCH_2Cl$	2	72	
	n-BuBr	2	86	58
	allylBr	2	75	
COOEt	EtBr	30	91	59
	EtI	30	94	
p-$NO_2C_6H_4$	Ph-$(CH_2)_3$-I	3.5	55	60
	Ph-$(CH_2)_8$-I	7	79	
p-$NO_2C_6H_4$	Ph-S-$(CH_2)_6$-Br	7	50	60
	Ph-S-$(CH_2)_8$-Br	7	59	

alkyl halides to give, exclusively, *N*-alkyl derivatives.[49,50] Such reactions were performed simply by mixing the azaheterocycle compound with 50% excess alkyl halide and a catalytic amount of TBAB. The reactants were adsorbed either on a mixture of potassium carbonate and potassium hydroxide or on potassium carbonate alone and then irradiated in a microwave oven for 30 s to 10 min to give the products with 70−95% yield. Also, selective N-alkylation of 6-amino-2-thiouracil with different halides was carried out efficiently (yield: 87−95%) by use of microwave-assisted methods in the presence of small amounts of DMF to improve energy transfer. No reaction was observed under the same conditions in a thermoregulated oil bath.[51] Eventually, a facile synthesis of a series of *N*-alkylpyrrolidino[60]fullerenes by solvent-free PTC under the action of microwaves has been described (Scheme 7).[52]

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

C-Alkylations of Active Methylenes. Several monoalkylations of functionalized acetates were described in a series of papers. The reactions were performed on potassium carbonate, either pure or mixed with potassium hydroxide. Some significant results are given in Table 4 (Scheme 8).

Scheme 8



Rapid monoalkylations are achieved in good yields compared to classical methods. Of particular interest is the synthesis of α-amino acids by alkylation of aldimines with microwave activation. Subsequent acidic hydrolysis of the alkylated imine provides leucine, serine or phenylalanine in preparatively useful yields within 1−5 min.[54]

Cyclopropane derivatives were obtained in a short reaction time (10 min) when reacting active methylene compounds (e.g., monomalononitrile) and 1,2-dibromoethane in the presence of Aliquat on potassium carbonate support using solvent-free PTC and microwave irradiation.[61] Alkylation of phenylacetonitrile was performed by solid−liquid PTC in 1−3 min under microwave irradiation.[62] The nitriles obtained were subsequently quickly hydrolyzed in a microwave oven to yield the corresponding amides or acids. It was found that functional groups can be selectively introduced at the C-2 position of isophorone via the epoxide ring-opening with several nucleophiles from active methylene groups. Different behavior was observed, depending on the reaction conditions and the nature of nucleophilic agents. The best experimental systems involved PTC or KF-alumina under solvent-free conditions and microwave irradiation[63]Scheme 9).

Condensation Reactions. Jasminaldehyde can be obtained classically by means of an aldol condensation reaction from

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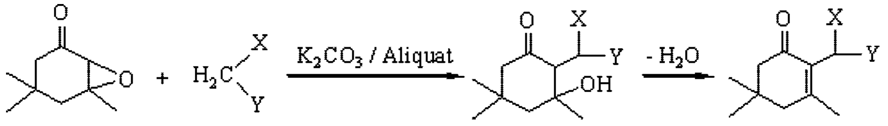
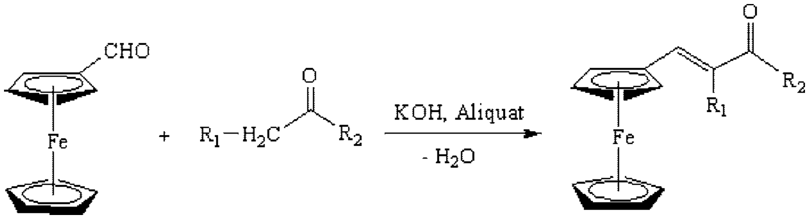
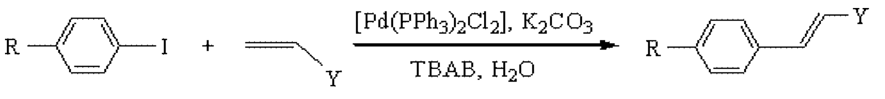
Scheme 9



Scheme 10



Scheme 11



Microwaves	10 min	86-93%
Conventional heating	10 min	5-15%
	3-7 h	54-90%

heptanal and benzaldehyde in 70% yield within 3 days at room temperature. By use of microwave irradiation, however, an enhanced yield of 82% was achieved in only 1 min in the presence of potassium hydroxide and Aliquat as a catalyst. Moreover, the amount of side products (self-condensation of *n*-heptanal) decreased from 30 to 18% when this technique was used.[64] By the same method, α-hexyl cinnamic aldehyde and chalcone were synthesized from octanal and acetophenone, respectively.[65] Another example of aldolization is the "dry" reaction of ferrocene carbaldehyde with carbonyl compounds in the presence of potassium hydroxide and Aliquat as a catalyst (Scheme 10).[66] Reactions which were too slow at room temperature are efficiently accelerated by use of microwaves, giving good yields within a few minutes.

Microwave activation and solvent-free PTC has been shown to be of prime efficiency for the synthesis of new benzylidene cineole derivatives (UV sunscreens) by the Knoevenagel reaction. When performed classically by use of potassium hydroxide in ethanol at room temperature for 12 h the yield was 30%. The yield was improved to 90−94% within 2−6 min under PTC conditions and microwave irradiation.[34]

In turn, the condensation of phenylacetonitrile with a series of substituted benzaldehydes was carried out in 3 min under microwave irradiation using potassium carbonate in the presence of TBAB as a catalyst. By extending the reaction time up to 10 min, four different stilbenes were obtained, owing to phenyl or nitrile group migration. These results were extended to a series of arylacetonitiriles with several aliphatic and aromatic aldehydes.[67] Recently, the preparation of α,α′-bis(benzylidene)cycloalkanones by the condensation of aromatic aldehyde with cyclopentanone and cyclohexanone in aqueous sodium carbonate solution and in the presence of TBAB as a catalyst was reported.[68] The reaction required only 30 s to 7 min of microwave irradiation and proceeded with 80 to 99% yield.

Heck and Suzuki Cross-Coupling Reactions. Reaction of organic halides with alkenes catalyzed by palladium compounds (Heck-type reaction) is known to be a useful method for carbon−carbon bond formation at unsubstituted vinylic positions. The first report on the application of microwave methodology to this type of reaction was published by Hallberg et al. in 1996[69] and then by Diaz-Ortiz et al. in 1997[70] in triethylamine solutions. Later, Villemin et al. studied the possibility of the Heck coupling reaction of iodoarenes with methyl acrylate in a water solution under pressurized conditions.[71] The reactions were carried out in a Teflon autoclave under microwave irradiation in the presence of palladium acetate, different phosphine-ligands, and tetrabutylammonium hydrogen sulfate (TBAHS) as a PTC catalyst to afford desired coupling products with 40−90% yield. More recently, the palladium-catalyzed Heck coupling reaction induced by microwave irradiation was reported under solventless liquid−liquid phase-transfer catalytic conditions in the presence of potassium carbonate and a small amount of [Pd(PPh$_3$)$_2$Cl$_2$]−TBAB as a catalyst.[72] The arylation of alkenes with aryl iodides proceeded smoothly to afford exclusively trans products in high yields (86−93%)Scheme 11).

Najera et al. carried out a number of the Heck reactions of deactivated aryl halides and styrenes under phosphane-free

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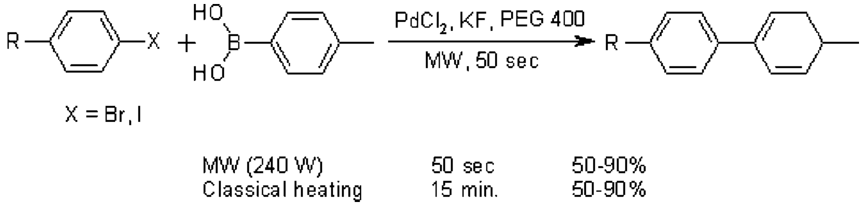
Scheme 12



conditions using oxime-derived palladacycles or palladium acetate as catalyst.[73] Coupling can be performed either with dicyclohexylmethylamine as base and TBAB as a PTC catalyst or in neat water with triethylamine in *N*,*N*-dimethylacetamide (DMA) solutions under microwave irradiation.

Recently, the scale-up protocol for the Heck coupling reaction between 4-bromoanisole and methyl acrylate under microwave irradiation was published.[74] The reagents were used in 1:2 stoichiometric ratio of aryl bromide (0.1 mol) to methyl acrylate (0.2 mmol), 1 equiv of TBAB as a phase-transfer agent, 3.7 of potassium carbonate as base, a palladium loading of 0.002 mol %, and water as the solvent. Temperature was ramped to 170 °C over the period of 5 min before holding it at this point for a further 15 min, stirring continuously. After cooling followed by collection and purification of the product, a quantitative conversion to 4-methoxycinnamic acid was obtained with an isolated yield of 93%.

Reaction of aryl halides with boronic acids catalyzed by palladium compounds (Suzuki reaction) is one of the versatile reactions for the selective formation of carbon−carbon bonds. One of the first reports on the application of microwaves to this type of reaction was published by Larhed et al. in 1996.[75] Subsequently, Varma et al. described the Suzuki-type coupling of boronic acids and aryl halides in the presence of palladium chloride and polyethylene glycol (PEG-400) under microwave irradiation (Scheme 12).[76] The reactions were performed at 100 °C to give the desired coupling products in 50−90% yield within 50 s. The coupling reaction can be also conducted under conventional conditions (oil bath, 100 °C), but to achieve similar yields longer reaction time was needed (15 min). It was found that addition of KF affords better yields.

Recently, Leadbeater et al. showed that the PTC protocol together with microwave irradiation can be used in preparation of biaryls using water, palladium acetate, and TBAB as a solvent, catalyst, and PTC agent, respectively.[77] The desired coupling products were obtained in good yields (60−90%). However, in this case, the reaction can be performed equally well using microwave and conventional heating methods. Although, it was later reported that Suzuki-type coupling of boronic acids and aryl halides was possible without the need for a transition-metal catalyst, the further reassessment of the reaction showed that ultralow palladium contaminants (∼50 ppb) either in commercially available and applied bases[78] or reaction vessels[79] were necessary to promote the reaction.

More recently, the Suzuki coupling reaction of phenylboronic acid and 4-bromotoluene carried out in an ethanol solution was scaled-up applying a continuous flow multimode microwave reactor.[74] For this purpose, ethanol was pumped through the microwave reactor vessel with the internal stirrer. The solvent was then heated to 150 °C. When the temperature and flow rate had stabilized at 150 °C and 40 mL/min (5 min residence time), respectively, the reaction solution was prepared. Thus, phenylboronic acid (39.6 g, 0.325 mol), 4-bromotoluene (42.5 g, 0.25 mmol), sodium hydroxide (2.0 M, 250 mL, 0.5 mol), ethanol (200 proof, 750 mL), and 1000 ppm Pd standard solution (10.0 mL, 94 μmol, 0.038 mol %) were thoroughly swirled until all of the starting materials had dissolved and then pumped through the reactor. The product solution collected was concentrated under reduced pressure to a total volume of approximately 500 mL and then poured into a separatory funnel containing diethyl ether (2 L) and water (1 L). The aqueous fraction was washed with additional diethyl ether (2 L). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure, to afford 4-methylbiphenyl as a white solid (34.8 g, 83% yield).[84]

Hantzsch Reaction. The synthesis of various substituted 1,4-dihydropyridines has been achieved by the reaction of aldehydes, ethyl/methyl acetoacetates, and ammonium acetate in water using a PTC conditions under microwave irradiation. This multicomponent reaction involving condensation of an aldehyde with dicarbonyl compounds and ammonia has attracted considerable attention due to the biological properties of many dihydropyridines. Compared to the classical Hantzsch reaction conditions, the microwave protocol consistently has the advantages of better yields and shorter reaction times (∼5−10 min). Bifunctional compounds containing two units have been synthesized using dialdehyde as a precursor in good yields (Scheme 13).[80]

Lately, the reaction was scaled up to 1 mol of an aldehyde, 3.4 mol of dicarbonyl compounds and 10 mol of ammonium hydroxide.[74] Performing the reaction in a 3 L flask and using water/ethanol as solvents, the reaction mixture was heated to reflux and held at this temperature until a total time of 20 min had elapsed. The synthesis was performed with two variations in substrates to confirm the generality of the procedure and obtained isolated yields ∼76% similar to those using small amount of reagents (i.e., 5 mmol of aldehyde).

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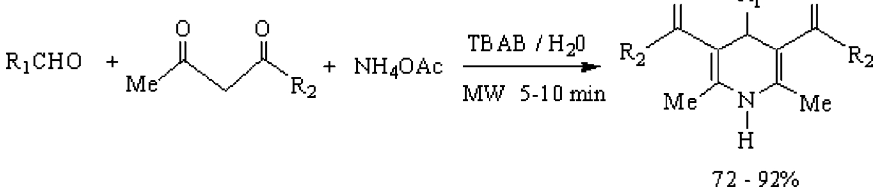
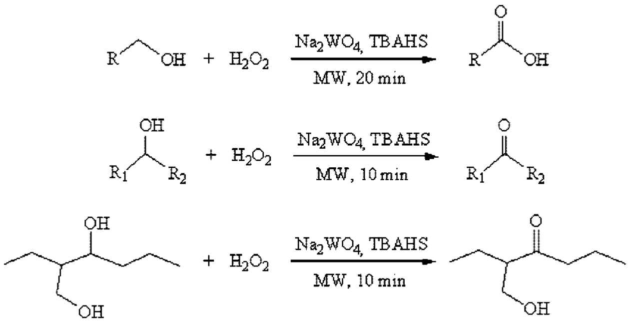
Scheme 13

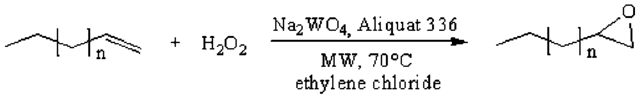


Scheme 14



Microwaves	10-20 min	60-97%
Conventional heating at 90°C	4 h	83-96%

Scheme 15



Microwaves	100 min	91-98%
Conventional heating	100 min	54-65%

Oxidation and Epoxidation Reactions. The application of microwave irradiation to the Noyori procedure of alcohol oxidation in the presence of hydrogen peroxide[81] resulted in the oxidation of primary and secondary alcohols to the equivalent carboxylic acids and ketones within 20−30 min under the action of microwave irradiation.[82] The reactions were performed under liquid−liquid PTC conditions using 30% aqueous H_2O_2 in the presence of sodium tungstate and tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst. The experimental procedure involves a simple mixing of an alcohol, $Na_2WO_4 \cdot H_2O$ and TBAHS then addition of 30% aqueous H_2O_2 in 25:1:1:125 molar ratios for primary alcohols and 25:1:1:40 molar ratios for secondary alcohols in an open vessel. The best results were obtained when the temperatures of reaction mixtures were 90 and 100 °C for primary and secondary alcohols, respectively (Scheme 14).

The oxidation of secondary alcohols under microwave irradiation can be also performed when hydrogen peroxide is substituted with hydrogen peroxide urea adduct (UHP).[83] The reaction results in appropriate carbonyl compounds in high yield and shortening of the reaction time, which was observed for microwave-assisted process compared to conventional conditions. Hydrogen peroxide has also been used with microwave irradiation for the epoxidation reactions of simple or cyclic alkenes. The reactions were accomplished under liquid−liquid PTC conditions in ethylene chloride solution in the presence of Na_2WO_4 and Aliquat 336 as catalysts. The best results were obtained at 70 °C when the concentration of hydrogen peroxide was set to 8% and the pH of aqueous phase was kept below 2 (Scheme 15).[84]

Recently, the Noyori oxidation procedure under PTC conditions was optimized for the oxidation of styrene and cyclohexene to benzoic and adipic acids, respectively.[85] The reactions were carried out in the presence of tetralkylammonium hydrogen sulfates and tungstate salts in the parallel synthesis setup for microwave irradiation. It was shown that through the optimization of microwave-assisted syntheses it seems possible to achieve advantages in time consumption and energy saving compared to a thermal reaction regime.

Polymerization Reactions. A number of polymers and polymeric materials can be successfully prepared, cross-linked, and processed under microwave irradiation.[5] Recently, the microwave-assisted protocol was applied to the synthesis of high-molecular weight (solid) epoxy resins.[86,87] The method is based on the polyaddition reaction of bisphenol A to a low-molecular weight epoxy resin or diglycidylether of bisphenol A in the presence of ammonium or phosphonium salts as well as imidazole derivatives (Scheme 16). The syntheses were also performed using conventional thermal heating (i.e., electric heating mantle) for the comparison of properties of high-molecular weight epoxy resins under both microwave and conventional conditions.

All the microwave reactions were carried out with 11.6 g of bisphenol A, 25.0 g of low-molecular weight epoxy resin (epoxy value = 0.57 mol/100 g), and a small amount of a catalyst. For microwave experiments, the flask was irradiated in a microwave reactor. The main advantage of the microwave process is 2-fold reduction of reaction time in comparison to conventional conditions. Number average molecular weight, weight average molecular weight, polydispersity index, epoxy value, and degree of branching of the resins were determined for both microwave and conventional conditions. It was found that the molecular weight distribution and degree of branching of the solid epoxy resins synthesized under microwave irradiation were comparable with those obtained under conventional heating and were not influenced by the reduction in reaction time. The same approach for the synthesis of solid epoxy resins

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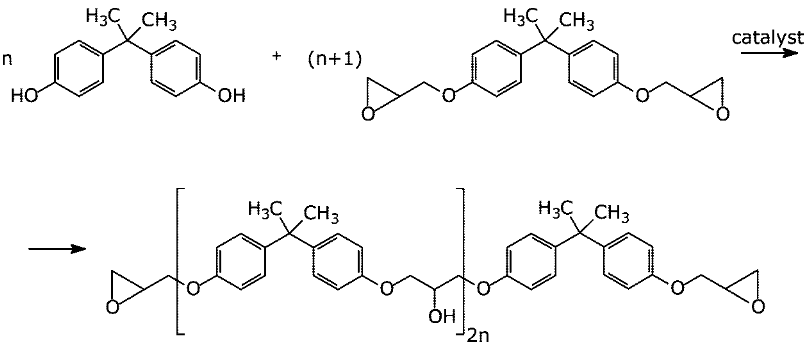
Figure 4. **Continuous microwave reactor with rotating quartz tube for the synthesis of high-molecular weight epoxy resin (Ertec, Poland).**

Scheme 16



with reduced flammability was also presented.[88] For this purpose, bisphenol A was either substituted or partially substituted with 1,1-dichloro-2,2-bis(4-hydroxyphenyl)ethylene, and the synthesis of solid epoxy resins was realized in the same manner as described previously.

More recently, the synthesis of high-molecular weight (solid) epoxy resins from bisphenol A and a low-molecular weight epoxy resin in a continuous microwave system that consists of four microwave cavities with a rotating quartz tube (2.0 m × 0.12 m) was tested and developed (Figure 4).[89]

All the microwave cavities are equipped with a continuous power regulation and temperature control, while each magnetron can be separately switched on and off if necessary, which offers the advantage of reduced power consumption compared to continuous power control. The speed of the quartz tube rotation is also continuously adjustable. It was shown that by applying the continuous microwave reactor it was possible to obtain high-molecular weight epoxy resins with an epoxy value of 0.11 mol of epoxy group per 100 g of resin by maintaining the flow of the substrates through the reactor at 8 kg/h. In one of the experiments, the product (epoxy resin) was not removed from the reactor during the run; i.e. the reaction mixture was "frozen" in the tube. Then, the resin samples were taken from different parts of the tube and analyzed for the conversion, i.e., epoxy values. It was found that the planned epoxy (i.e., 0.11 mol/100 g) value was reached in the middle distance from the tube beginning, which means that the reactor can even work at flow rates higher than 8 kg/h.[89]

The synthesis of linear polyethers either from isosorbide or isoiodide (important byproduct of corn starch industry) and alkyl dibromides or dimethanesulfonates by using microwave irradiation under solid−liquid PTC conditions was described by Loupy et al. (Scheme 17).[90,91]

The reactions were carried out in a single-mode microwave reactor with temperature infrared detector, which was previously calibrated with a fiber-optic detector introduced into the reaction mixture. The reaction mixtures consisting of 5 mmol of isosorbide or isoiodide, 5 mmol alkyl dibromide/dimesylate, 1.25 mmol of TBAB and 12.5 mmol of powdered potassium

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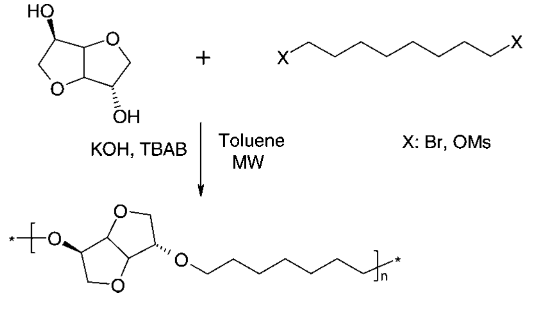
Scheme 17



hydroxide were irradiated for 30 min to afford the polyethers in 70−90% yield. It was found that the use of a small amount of solvent was necessary to ensure a good temperature control and a decrease in the viscosity of the reaction medium. In the case of isosorbide, the microwave-assisted synthesis proceeded more rapidly, compared with conventional heating, and was reduced to 30 min with yields of 69−78%. Under conventional conditions, the polyethers were made in 28−30% yield within 30 min. Similar yields of the polyethers were obtained when the reaction time was extended to 24 h. They remained practically unchanged even though the synthesis was held for 7 days. The analysis of properties of the synthesized polyethers revealed that the structure of the products strictly depended on the activation mode (microwave or conventional activation). Under microwave conditions, the polyethers were characterized by higher molecular weight and better homogeneity. For example, within 30 min of reaction time under conventional heating, the polyesters with higher molecular weight were not observed at all. Moreover, it was found that the chain terminations were different under microwave and conventional conditions. The polyesters prepared with conventional heating have shorter chains with terminal hydroxyl ends, whereas under microwave irradiation the polymer chains were longer with terminal ethylenic ends. In fact, under microwave irradiation, terminal ethylenic ends were formed rapidly and set up a hindrance to further polymer growth. In comparison, under conventional conditions the terminations were essentially constituted by hydroxyl functions; however, further polymerization was terminated.

Later, the same protocol was applied to the polycondensation of aliphatic diols of isosorbide with 1,8-dimesyloctane and other dialkylating agents (Scheme 18).[92] In all cases, microwave-assisted polycondensations proceeded more efficiently compared to conventional heating (the reaction time was reduced from 24 h to 30 min: ratio 1/50). The polycondensation under microwave conditions yielded 63% of polyethers with relatively high average-weight molecular weights (up to 7000 g/mol). The polyethers were characterized by ^{1}H and ^{13}C NMR, FT-IR spectroscopy, SEC measurement and MALDI-TOF mass spectrometry.

Conclusion

As has been demonstrated, the coupling of microwave technology and PTC conditions creates a clean, selective and efficient methodology for performing certain organic reactions with substantial improvements in terms of mild conditions and simplicity of operating procedures. The application of microwave irradiation to provide the energy for the activation of chemical species certainly leads to faster and cleaner reactions when compared to conventional heating. Solvent can often be excluded from the reaction when the electrophile is a liquid and can therefore act both as a reagent and the organic phase. This has impact for green chemistry considerations.[97]

Significant improvements in the yields of PTC-catalyzed reactions and/or reaction conditions can be generally achieved, together with considerable simplification of operating procedures. The powerful synergistic combination of PTC and microwave techniques has certainly enabled an ever increasing number of reactions to be conducted under cleaner and milder conditions. The inherent simplicity of the method can furthermore trigger the development of new protocols for industrial applications. As it was shown in this review, a number of PTC procedures run under microwave irradiation can be scaled from small-scale synthesis (grams) through the multigram level (100−300 g) to kilogram level protocols. These examples cited herein related to PTC protocols include:

(1) alkylation of carboxylic acids (200−300 g);[17]

(2) Heck reaction (10−20 g);[74]

(3) Suzuki coupling (40−60 g);[74]

(4) synthesis of high-molecular weight epoxy resins (100−8000 g).[89]

Other examples of scaling up reaction procedures under microwave irradiation can be found in the literature.[17,74,93–96] In the future, many companies that specialize in microwave power will build microwave equipment to customer specifications. Once the industry begins to manufacture more equipment amenable to plant operation, we expect to see a significant increase in the production of multikilogram quantities of products made with PTC and microwave technology.

We expect this list to increase significantly as the power of combining the concepts of PTC and microwave technology is appreciated by scientists. For example, over the next 5 years, the market for microwave instruments for chemical analysis and chemical synthesis is predicted to grow at a CAGR (i.e., the year-overyear growth rate of an investment over a specified period of time) of 9.6% per annum, to reach $145.8 million (USD) by 2008. The chemical synthesis market will give a major thrust to the microwave chemistry market, which is expected to grow at a CAGR of 20% per year, to $67.2 million (USD) by 2008. As the analytical segment has matured, it is predicted to show a stable CAGR of about 5% per year, reaching 78.6 million USD during the same period. In the next 5−6 years, the chemical synthesis segment is expected to overtake the analytical segment in terms of market share. This

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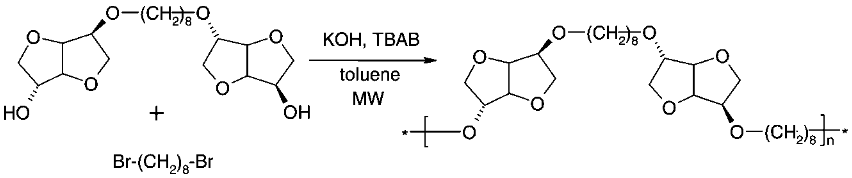
Scheme 18



is primarily due to the increasingly successful implementation of microwave instruments in chemical synthesis. Another contributor will be the growing research and intellectual property activity in the segment, such as research on the scaling up of reactions.[98]

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