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Organic Sonochemistry: Ultrasound in Green Organic Synthesis

The evolution of chemistry, particularly organic chemistry, has had a serious impact in the 20th Century, from the health sector for the production of medicines, to the perfumes and clothing sector for the manufacture of dyes and textiles. While chemistry is at the root of extraordinary improvements in people's living conditions, its image has gradually deteriorated as a result of incidents and accidents with dramatic ecological and/or human consequences. A global awareness of the impact of human activities on the environment has given rise to the neologism of sustainability. The concept of "green chemistry" or "sustainable chemistry" was first developed in the United States in the early 1990s with the objective of defining rules to pollution prevention related to chemical activities. These concepts led to the edition of 12 principles – often refered to as "the twelve principles of Green Chemistry".

Among the activation techniques available to meet this new paradigm, the extraordinary properties of ultrasound and sonochemistry play an important role. Indeed, sonochemistry is simple to use, and allows chemical reactions to be carried out under ultrasound, sometimes preventing the need for external heat, reagents

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or catalysts, leading to high yields and the production of a minimum amount of waste.

From the discovery of ultrasound to its use in green organic chemistry, this chapter provides an overview of the main applications of sonochemistry in organic chemistry and especially in “green organic chemistry”, with a particular focus on the work published in the literature in recent years including some elements on ultrasound theory and the equipment used to produce it.

1.1. Introduction: history of ultrasound, organic sonochemistry and early work

While some butterflies imagine escaping their vampire predators by engaging in complicated aerial figures, others produce ultrasounds that repel these fearsome chiroptera, thus informing them that dinner looks detestable (Gouaillier 2001). While this story is 56 million years old between butterflies and bats, humankind did not learn to use ultrasound reliably until the early 20th Century.

1.1.1. *The history of ultrasound and organic sonochemistry*

Between 1793 and 1798, Father Lazzaro Spallanzani (1729–1799) and his colleague Doctor Louis Jurine (1751–1819) suspected the existence of ultrasound by observing that bats orient themselves in darkness without any difficulty. In 1880, Marcellin Berthelot wrote that “a multitude of chemical transformations are attributed today to the energy of ethereal matter, animated by these vibratory and other movements that produce calorific, luminous and electrical phenomena” (Berthelot 1880). In 1883, physiologist Francis Galton (1822–1911) discovered them by inventing the “ultrasonic whistle”. Nevertheless, it was the discovery of piezoelectricity in 1880 by the brothers Pierre (1859–1906) and Jacques (1856–1941) Curie, which made it possible after 1883 to produce and to use ultrasound easily and repeatedly. Paul Langevin (1872–1946) then had the idea of applying the phenomenon of piezoelectricity to the production and reception of ultrasound. After the tragedy of the

Titanic in 1912, he proposed their use for iceberg detection. Then, in 1915, during the First World War, he developed a way to detect submarines by means of ultrasound; and in 1917, together with the engineer Constantin Chilowski, he invented the ASDIC (Anti-Submarine Detection Investigation Committee), an ancestor of Sonar, thus opening a field of industrial applications to these vibrations undetected by the human ear. The large number of fundamental discoveries between 1920 and 1939, as well as the technical improvements made, particularly concerning vibration converters, paved the way for the industrial development of ultrasound in cleaning, welding, drilling and medical applications. In 1951, J.J. Wild (1914–2009) and J. Reid (1926) developed the first ultrasound scanner for brain tumor research; it is now mainly used in obstetrics.

At the same time, studies have shown that ultrasound can change the medium in which it propagates and the work of Robert William Wood (1868–1955) and Alfred Lee Loomis (1887–1975) in biology and that of Theodore William Richards (1868–1928) and Alfred Lee Loomis in chemistry are generally considered as the first sonochemical experiments (Richards and Loomis 1927; Woods and Loomis 1927).

In 1928, Edmund Newton Harvey (1887–1959) and Alfred Lee Loomis observed, among other things, the destruction of frog blood cells irradiated by high frequency ultrasound (Harvey and Loomis 1928).

In 1933, Sándor Szalay showed that at an ultrasound frequency of 722 kHz can depolymerize starch, gum arabic and gelatin, thus reducing their viscosity (Szalay 1933; Szent-György 1933).

The same year, Earl Flosdorf and Leslie Chambers (1933) described the action of ultrasound for instant coagulation of proteins, oxidation of inorganic halides to dihalogens and hydrogen sulfide to sulfur by molecular oxygen.

They continued this work by studying the denaturation of proteins under ultrasound (Chambers and Flosdorf 1936), which they explained via the direct transfer of energy from the gases present to the protein molecules, without chemical intervention.

One year later, H. Frenzel and H. Schultes observed the luminescence emitted by water subjected to ultrasound during an experiment on Sonar (Frenzel and Schultes 1934).

E. Newton Harvey (Harvey 1939), P.O. Prudhomme (Prudhomme 1957) and R.H. Busso (Prudhomme and Busso 1952) and many others (for instance Griffing and Sette 1955) later carried out research dedicated to understanding this phenomenon.

In 1937, Sven Brohult carried out the partial fractionation of the hemocyanins of *Helix pomatia*, a Burgundy snail, by subjecting diluted solutions of their metalloproteins to ultrasound at a frequency of 250 kHz. He thus obtained uniform fragments 1/2 and 1/8 length of the initial molecule and observed an increase in the temperature of the medium (Brohult 1937).

In 1960, J. Giuntini and his collaborators (Hannoun *et al.* 1960) studied the action of ultrasound on the influenza virus, inactivating its infectious power while activating the vaccinating power.

1.1.2. *Pioneering work in organic sonochemistry*

It was not until the 1950s, with the development of more reliable ultrasonic generators, that researchers became interested in the effect of ultrasound for organic synthesis. Indeed, the main objective of the first studies carried out in organic sonochemistry was to study the effect of ultrasound on organic molecules in an aqueous medium (Zechmeister and Wallcave 1955; Zechmeister and Curelle 1958; Currelle *et al.* 1963) and not their use for organic chemical reactions.

For example, S. Prakash and J.D. Pandey (Prakash and Pandey 1965) studied the sonolysis of aliphatic and aromatic halogen compounds. They observed that iodobenzene and *ortho-*

dichlorobenzene produce hydrogen halides while ethyl iodide releases molecular iodine. They also studied the kinetics of ultrasonic cleavage reactions and showed that the amount of halogen released increases with the duration of ultrasonic irradiation. In addition, the amount of free halogen increases up to a certain irradiation time beyond which a plateau is reached or a decrease is observed. Based on the knowledge of the phenomenon of transient acoustic cavitation (section 1.2.1.2), the authors proposed a mechanism for the formation of the various products of halocarbon sonolysis in aqueous media (Figure 1.1). The decomposition of water molecules is the main cause of the transformation of solute molecules. When ethyl iodide, iodobenzene and orthodichlorobenzene are decomposed, two primary reactions occur simultaneously (1). The decomposition of water mainly leads to the production of $H^{\cdot}$ and $OH^{\cdot}$ radicals$^{\cdot}$ (1). Hydrogen peroxide is formed by the recombination of $OH^{\cdot}$ radicals but also via the mechanism (2) in an oxygenated environment. The release of halogen radicals can occur according to mechanisms (3), (4) and (5). Since the energy of the C-I bond is lower than the ones of the C-Br and C-Cl bonds, the C-I bond is probably easily cleaved by the available ultrasonic energy. The activated oxygen generated oxidizes the alcohol to an aldehyde, which is then over-oxidized to a carboxylic acid (6). Acetylene and diacetylene being formed, as already observed by other authors (Zechmeister and Wallcave 1955; Zechmeister and Curelle 1958; Currell *et al.* 1963), are from the decomposition, caused by acoustic cavitation, of iodobenzene, phenol and *o*-dichlorobenzene, or from their depolymerization (7). Dichlorobenzene leads to the formation of chlorophenol, hydrochloric acid and catechol (5).

Subsequently, experiments were carried out by L.A. Spurlock and S.B. Reifsneider (1970) to investigate and understand the mechanisms of chemical transformations of simple molecules such as dibutyl sulfide when subject to ultrasound. The irradiation of dibutyl sulfide, in water and under argon atmosphere, at a frequency of 800 kHz primarily leads to the formation of dibutylsulfoxide, *n*-butane-sulfonic acid and traces of butanoic acid in the aqueous phase. The analysis of the gas phase reveals the presence of carbon monoxide, methane, ethylene and acetylene, of which butanal would be the probable precursor. The authors were able to propose a mechanism for the transformation of dibutyl sulfide under ultrasonic irradiation (Figure 1.2).

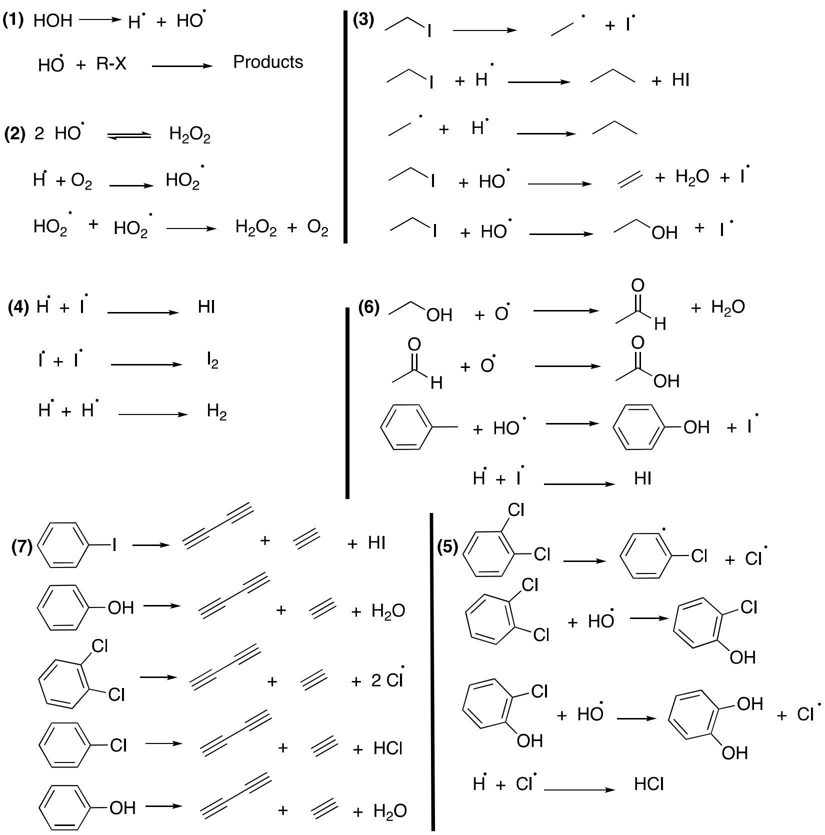


Figure 1.1. *Hypotheses of the mechanism of the sonolysis of haloalkanes (adapted from Prakash and Pandey 1965)*

The authors then continued their research by studying the behavior of a series of aliphatic aldehydes and carboxylic acids, irradiated at a frequency of 800 kHz and an intensity of 9.4 W/cm^2, in the presence of argon or molecular oxygen (Reifsneider and Spurlock 1973) (Figure 1.3).

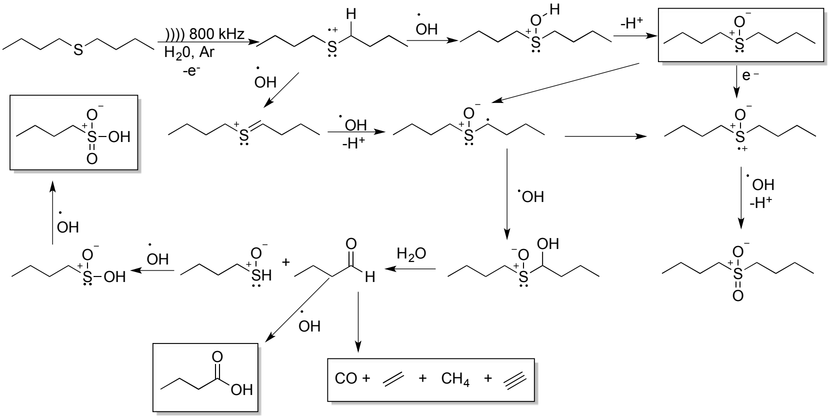


Figure 1.2. *Hypothesis of the mechanism of transformation of dibutyl sulfide under ultrasonic irradiation (adapted from Spurlock and Reifsneider 1970)*

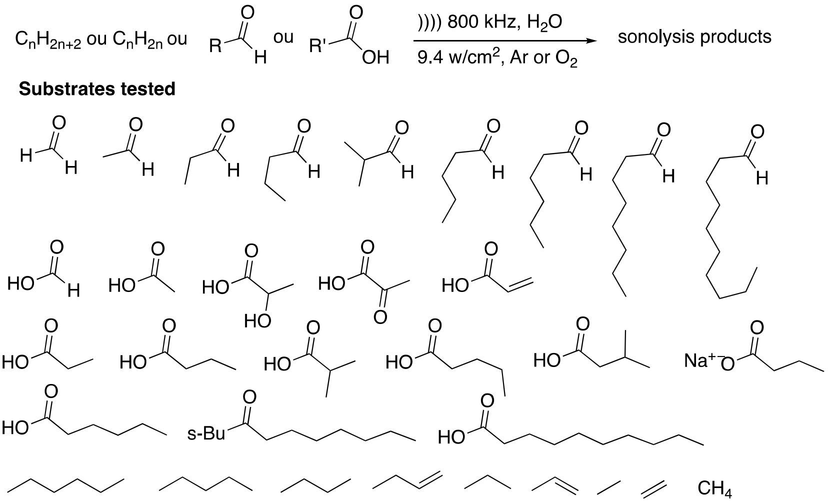


Figure 1.3. *Study of the sonolysis of organic compounds at a frequency of 800 kHz and an acoustic power of 9.4 W/cm^2 (adapted from Reifsneider and Spurlock 1973)*

The results showed that, in water and under ultrasonic irradiation, aliphatic aldehydes were both oxidized to carboxylic acids and fragmented into C1 and C2 volatile organic compounds (VOC). Aliphatic carboxylic acids, which are more stable under the action of ultrasound, fragmented in a smaller proportion. The authors attempted to draw a parallel with their previous study on dibutyl sulfide. The molecules studied contained from 1 to 10 carbons and were sometimes branched or di-functionalized; reactions that took place under ultrasound followed different simultaneous reaction paths and were therefore extremely complex. However, they noted the influence of the nature of the chemical function of the molecule or family that it belonged to on its stability under ultrasound irradiation.

In conclusion, this study made it possible to define certain guidelines for greater predictability of the mechanisms induced by ultrasound during the irradiation of organic molecules in an aqueous medium.

W.H. Staas and L.A. Spurlock (Staas and Spurlock 1975) then investigated the effects of ultrasound on amino acids and performed a detailed analysis of their sonolysis products. Thus, nine amino acids were irradiated at a frequency of 800 kHz under Ar atmosphere for six hours (Figure 1.4).

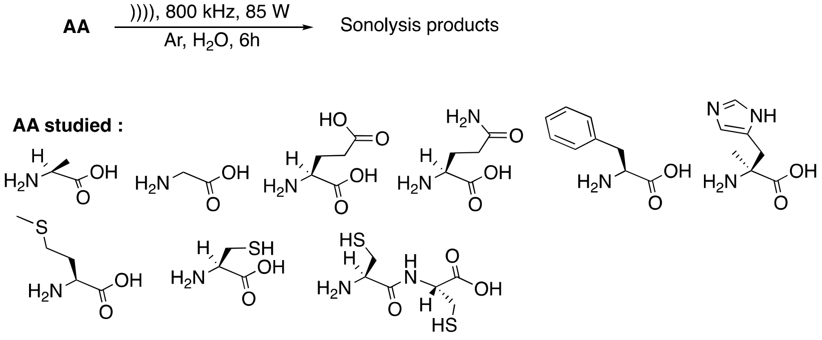
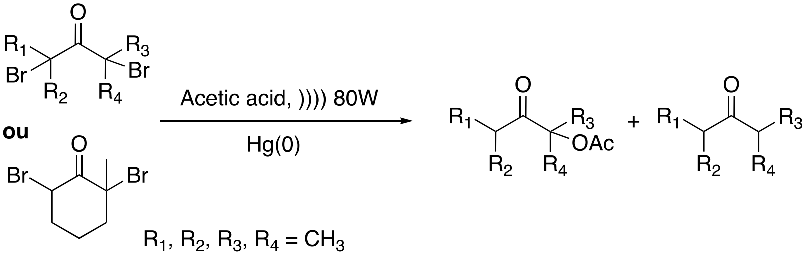


Figure 1.4. *Study of sonolysis products of 9 amino acids at a frequency of 800 kHz and a power of 85 W (adapted from Staas and Spurlock 1975)*

Glycine and alanine are the most stable amino acids under ultrasonic irradiation, resulting in ammonia, carbon monoxide and formaldehyde. The formation of glycolic and lactic acids is attributed to the deamination of glycine and alanine. The presence of acetaldehyde in alanine and phenylacetaldehyde samples in phenylalanine samples after irradiation suggests the formation of aldehydes by irradiation of amino acids in general, via deamination and decarboxylation. The glutamine amide unit appears to be very stable against ultrasound and a very low proportion of glutamic acid deamination is observed. Similarly, the loss of a CH_2 from the distant carboxylic functional group of glutamic acid that leads to aspartic acid is very slow. Sulfur-containing amino acids undergo the expected reactions under oxidizing conditions. Cysteine is converted into cystine and cysteic acid is formed from both cysteine and cystine. The quantities of these sonolysis products are in accordance with the usual oxidation sequence of thiols to sulfonic acids. Hydrogen sulfide and serine are formed from cysteine. Surprisingly, methionine is only slightly more unstable under ultrasonic irradiation than histidine and phenylalanine. Formaldehyde production is higher from methionine than from any other amino acid. Formaldehyde could be formed by hydroxylation and removal of the terminal *S*-methyl group. The methane and methanol observed appear to come from the same source. The authors also observe polymer formation as a result of the pH of the aqueous phase.

In conclusion, given the high stability of the amide bond of glutamide, the authors planned to investigate the stability of the peptide bond in future work.

Since then, work describing the use of ultrasound for organic chemistry applications has appeared in the scientific literature. For example, in 1978, A.J. Fry and D. Herr described the reduction of α,α'-dibromoketones in a protic solvent by ultrasonically dispersed mercury (Fry and Herr 1978). Indeed, the authors show that α,α'-non-benzyl dibromoketones cannot be reduced by mercury unless it is in a finely dispersed state. For this purpose, an ultrasonic bath (section 1.3.1) was used at a power of 80 W and 25°C (Figure 1.5).



$R_1, R_2, R_3, R_4 = CH_3$
$R_1, R_2 = H, R_3 = CH_3, R_4 = CH_2CH_3$
$R_1, R_2, R_3 = CH_3, R_4 = H$
$R_1, R_2 = CH_3, R_3 = H, R_4 = CH_2CH_2CH_3$
$R_1, R_3 = H, R_2, R_4 = CH_2CH_2CH_3$

Figure 1.5. *Reduction of α,α'-dibromoketones in acetic acid by mercury dispersed under ultrasonic irradiation (adapted from Fry and Herr 1978)*

Given the electrochemical potentials of mercury and dibromoketone, the reduction seems surprising. Nevertheless, the authors explain it, among other things, to be due to a shift in the electrochemical potential of the Hg(0)/Hg(II) couple towards negative potentials due to the coordination of mercury with the enolate anion (Figure 1.6).

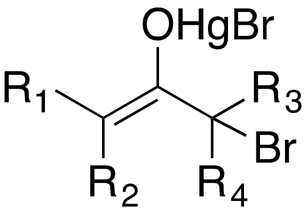
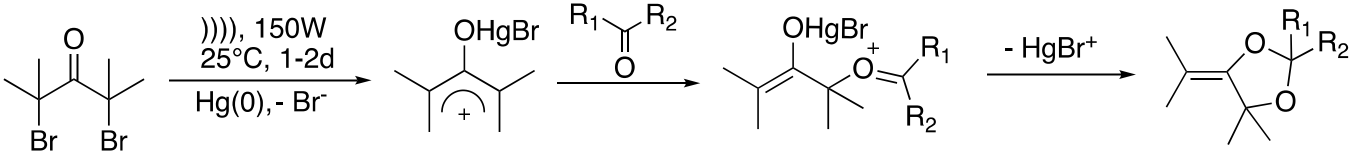


Figure 1.6. *Coordination of mercury with the enolate anion (adapted from Fry and Herr 1978)*

Similarly, A.J. Fry *et al.* (1978) describe the reduction of α,α'dibromoketones by ultrasonically dispersed mercury for the synthesis of 4-isopropylidene-1,3-dioxolanes. A mechanism was proposed by the authors (Figure 1.7).



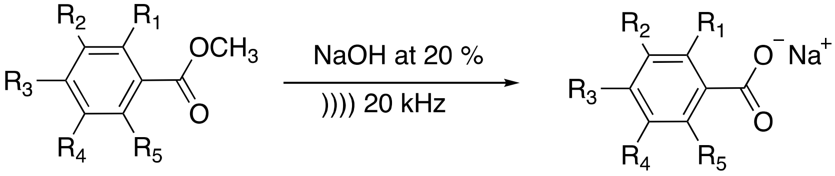
R_1, R_2 = Me ; R_1 = Me, R_2= Et ; R_1, R_2 = Et ; R_1 = Me, R_2= Pr^i

Figure 1.7. *Proposed mechanism of the reduction of α,α'-dibromoketones by ultrasonically dispersed mercury for the synthesis of 4-isopropylidene-1,3-dioxolanes (adapted from Fry* et al. *1978)*

Even if yields are modest, the reaction is very simple to perform experimentaly and allows the formation of original 4-methylene-1,3-dioxolane cyclic systems in a single step.

In the two previous examples, the authors explain their results by a fine dispersion of the catalyst under ultrasonic irradiation, involving the physical effects of ultrasound.

In the following year, S. Moon, L. Duchin and J.V. Cooney (Moon *et al.* 1979) proposed the saponification of carboxylic acid esters catalyzed by ultrasound at a frequency of 20 kHz (Figure 1.8).



$R_1, R_2, R_3, R_4, R_5 = H$; $R_1, R_3, R_5 = CH_3, R_2, R_4 = H$
$R_3, R_5 = CH_3, R_1, R_2, R_4 = H$; $R_1, R_3, R_5 = H, R_2, R_4 = CH_3$

Figure 1.8. *Saponification of aromatic carboxylic acid esters under ultrasonic irradiation (adapted from Moon* et al. *1979)*

The use of ultrasound reduces the duration of the methyl benzoate saponification reaction by a factor of 9 compared to silent conditions; 97% yield in benzoic acid is obtained after 90 minutes under reflux compared to 98% after 10 minutes under ultrasonic irradiation. Saponification of methyl 2,4,6-trimethylbenzoate is impossible, even after 10 minutes or 60 minutes of ultrasonic irradiation. Methyl 2,4-dimethylbenzoate is saponified with a yield of 94% in 60 minutes under ultrasonic irradiation, while 90 minutes under reflux only leads to 15% of the corresponding carboxylic acid. A yield of 96% is obtained after 90 minutes of ultrasonic irradiation of methyl 3,5-dimethylbenzoate while 90 minutes under reflux leads to only 71% of the expected carboxylic acid. The authors attribute these excellent results, when ultrasound is used, to the generation of emulsion under ultrasonic irradiation and not to the heating of the medium.

In summary, ultrasound catalyzes the saponification of aromatic esters in a biphasic medium.

In 1980, J.-L. Luche and J.-C. Damiano (Luche and Damiano 1980) published the preparation of organolithians and magnesium under ultrasonic irradiation at a frequency of 50 kHz and a power of 60 W for the synthesis of alcohols via the Barbier reaction (Figure 1.9).

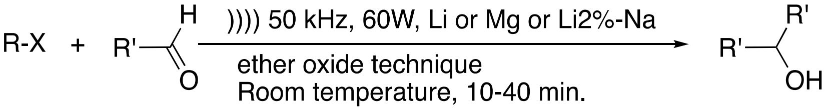


Figure 1.9. *Barbier reaction under ultrasonic irradiation (adapted from Luche and Damiano 1980)*

Thus, *n*-propyl-, *n*-butyl- and phenyllithium bromides were prepared with yields of 90, 61 and 95% respectively and in relatively short times compared to isopropyl and tert-butyllithium bromides, which required more than one hour. Nevertheless, the interest of ultrasound was highlighted in the Barbier reaction, which was carried out in non-anhydrous, technical grade THF. All reactions were conducted in less than 1 hour and often in 10 to 15 minutes. The secondary reactions usually observed, such as reductions and enolizations, were significantly reduced. The condensation of benzyl bromide with acetophenone leads to the expected product while under silent conditions the Wurtz coupling predominates with benzyl halides. In the presence of allylic and vinyl bromides and under ultrasound, the reaction is clean and yields are high. The authors could not explain the effect of ultrasound on the formation of organometallic reagents; however, they suggested a positive alteration of the metal surface due to the mechanical effects of ultrasound. Ultrasound seems to keep the surface of the metal free of derived species such as organolithium, lithium halide or hydroxide, thus keeping it active.

In conclusion, the authors proposed an effective method for the Barbier reaction which operating conditions, involving a non-anhydrous solvent at room temperature, would make it recoverable at an industrial scale.

In the same year, Neppiras (1980) used the term sonochemistry for the first time. Sonochemistry describes the chemical and physical processes that occur in solution thanks to the energy provided by the ultrasonic waves that propagate through it. In the 1980s, there was a real increase in the number of publications describing reactions of organic compounds occurring in organic solvents and under ultrasound.

1.2. Some elements of ultrasound theory

Sound is a wave produced by the mechanical vibration of a fluid or solid support and propagated by the elasticity of the surrounding medium in the form of longitudinal waves (Figure 1.10).

The sound spectrum is divided into four intervals defined according to the frequency of the emitted wave:

– infrasound with a frequency range between 0 and 16 Hz;

– audible sounds with a frequency range between 16 Hz and 16 kHz;

– ultrasound with a frequency range between 16 kHz and 10 THz;

– hypersound with frequencies above 100 GHz.

Ultrasound extends from the frequency limit of audible sounds, about 16 kHz, to the thermal agitation frequencies of molecules, about 10 THz (Figure 1.11).

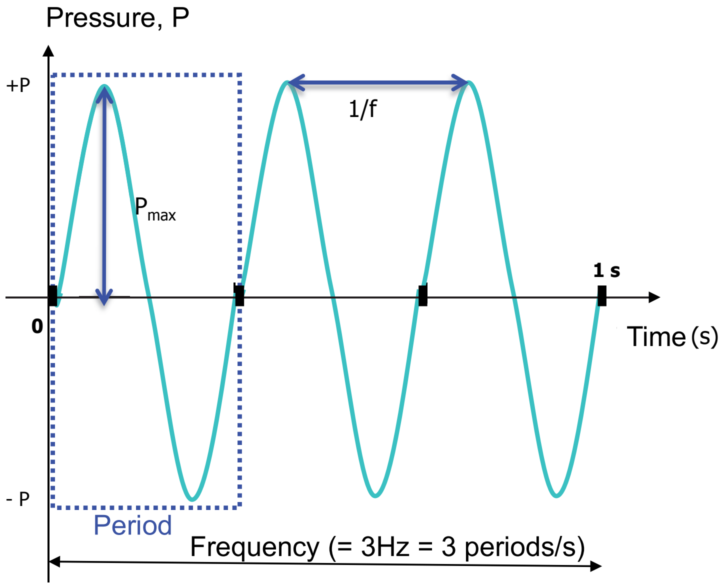
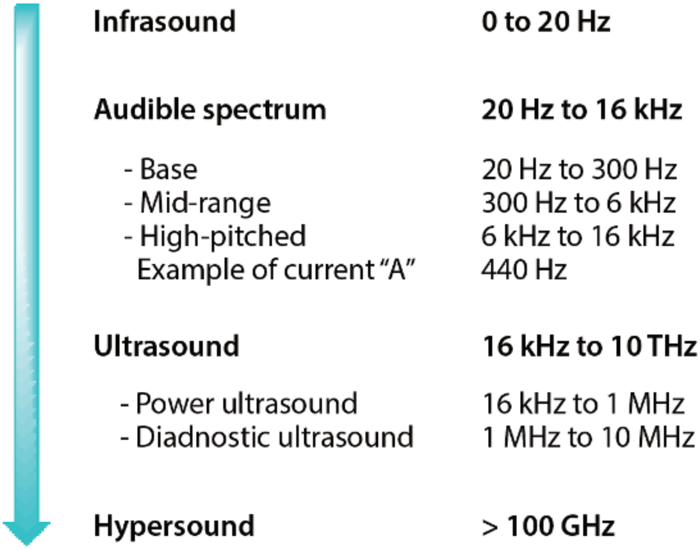


Figure 1.10. *Propagation of a sound wave in a liquid medium. For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*



Infrasound	**0 to 20 Hz**
Audible spectrum	**20 Hz to 16 kHz**
- Base	20 Hz to 300 Hz
- Mid-range	300 Hz to 6 kHz
- High-pitched	6 kHz to 16 kHz
Example of current "A"	440 Hz
Ultrasound	**16 kHz to 10 THz**
- Power ultrasound	16 kHz to 1 MHz
- Diadnostic ultrasound	1 MHz to 10 MHz
Hypersound	**> 100 GHz**

Figure 1.11. *Scale of sounds as a function of frequency*

Ultrasound has many applications depending on the frequency; power ultrasound is generally used in chemistry. Indeed, in the broad spectrum of ultrasound, two domains are typically differentiated:

– 16 Hz to 1 MHz corresponds to the range of power ultrasound, characterized by high intensity and low frequency. In this range, the ultrasonic wave changes the medium in which it propagates;

– 1 MHz to 10 MHz corresponds to the diagnostic ultrasound range, characterized by low intensity and high frequency. In this range, the ultrasonic wave is modified by the medium in which it propagates.

Ultrasound is a wave, propagating in an elastic medium, which has all the general properties of periodic progressive waves such as propagation, attenuation and reflection. Thus, a pressure wave is classically characterized by its frequency f and its amplitude P. Equation [1.1] describes in a simplified way the temporal evolution of the pressure P(t) at a given point in an elastic medium such as water during the passage of the ultrasonic wave:

$$Pt = Pmax \sin (2\pi + \varphi) \qquad [1.1]$$

with:

– $Pmax$: maximum amplitude;

– t: time;

– φ: phase.

The frequency f of a pressure wave can be expressed as a function of its wavelength and sound velocity ([1.2]):

$$f = c/\lambda \qquad [1.2]$$

with:

– c: speed of sound (1,403 m/s in pure water at 0°C and a pressure of 1 atm) (Greenspan and Tschiegg 1957; Chen and Millero 1976);

– λ: wavelength (m).

Thus, under normal conditions of temperature and pressure, an ultrasonic wave with a frequency of 20 kHz propagates in pure water with a wavelength of 0.07015 m while at a frequency of 1.6 MHz its wavelength is only 0.00087688 m.

These waves obey the general laws on sinusoidal waves and propagate through elastic media (gas, liquid, solid) with a velocity (c in m/s) that is a function of the density and elasticity of the medium traversed. Thus, the ultrasound velocity at 20°C in humid air is 340 m/s while it is 1,482 m/s in pure water at the same temperature. Indeed, the denser the medium is, the higher its velocity is. Moreover, for the same pressure value, the velocity decreases as the temperature decreases; it increases from 1,482 m/s in pure water at 20°C to 1,403 m/s at 0°C at a pressure of 1 atm.

The acoustic impedance of a medium for a sound wave reflects the specific resistance of the medium to its propagation. It is the product of the density of the medium irradiated by the speed of the wave that propagates it. During its propagation, the wave does not conserve its energy, which is dissipated and decreases as it moves further away from the ultrasonic source: this is attenuation of the ultrasonic wave.

1.2.1. *Bubble dynamics*

By focusing high intensity ultrasonic waves in a liquid, thousands of small bubbles appear. This process of liquid dislocation is called acoustic cavitation. Bubbles form a fractal structure (Parlitz *et al.* 1995) that evolves dynamically over time. They also emit a muted and chaotic sound due to their non-linear oscillations forced into the sound field.

Depending on its origins, cavitation can be thermal, optical, hydrodynamic or acoustic; it can even be initiated by particles such as neutrons (Shapira and Saltmarsh 2002).

The cavitation phenomenon was first described in 1895 by John Thornycroft and Sydney Barnaby (1895) who noted that the abnormal vibrations of their submarine propeller were due to the implosion, under water pressure, of large bubbles generated by the movement of the blades. Lord Rayleigh, in 1917, published the first mathematical model describing cavitation in an incompressible fluid (Rayleigh 1917). Nevertheless, it was in the 17th Century (1661–1662) that Christiaan Huygens (Kell 1983) discovered that liquid water can exist in a metastable state at a pressure below its vapor pressure.

In a liquid medium, the action of ultrasound is essentially based on the phenomenon of cavitation, which describes the radial oscillation of a gas and/or vapor bubble (Figure 1.12). The term “cavitation” is nevertheless reserved for cases where both expansion and compression phases are present.

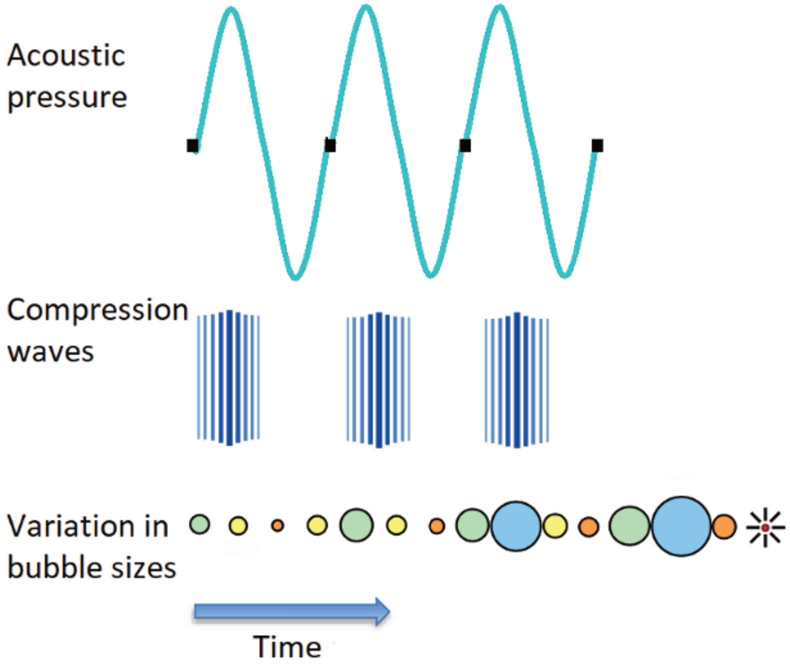


Figure 1.12. *Simplified representation of the acoustic cavitation phenomenon. For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*

Acoustic cavitation in a moving liquid corresponds to the formation of cavities, filled with gas and/or liquid vapor, when the pressure at a point in the liquid becomes lower than its saturating vapor pressure. If the pressure variation responsible for bubble growth is caused by a high intensity sound, usually a high-power sound field, the term “acoustic cavitation” is used. Also, the energy supplied must be sufficient to overcome the cohesive forces of the liquid and the depression necessary for the appearance of bubbles depends both on the properties and on the purity of the liquid. In pure liquids, these cohesion forces are extremely strong, and they are weakened by the nuclei of gases or impurities that may be present. Generally speaking, liquids have enough impurities to allow cavitation to occur. The bubbles of a few micrometers in diameter that then appear in the liquid are in turn subjected to ultrasonic excitation that triggers their growth, oscillation and, under certain conditions, implosion.

Two mechanisms are proposed to explain the formation of bubbles (Young 1989). One of them involves pre-existing bubbles in the liquid, protected from dissolution by a “skin” made up of organic impurities. A second mechanism is based on the existence of solid particles in the liquid that traps gases, sites of nucleation. Since the pressure inside the gas cavity is lower than that of the liquid, the gas diffuses into the cavity, causing it to grow. A bubble is thus created until the gas escapes under the influence of a radiantion force.

A formed bubble, according to one of the two mechanisms previously described, enlarges to a critical size: the resonance size, which depends on the frequency of the ultrasonic field. When bubbles reach their resonance size, via processes called rectified diffusion or coalescence, two events can take place. For a given pressure variation amplitude, there is a resonance frequency for which the amplitude of the bubble vibrations is at its maximum. It is a simple relationship that links the resonance size of the bubble to the frequency (equation [1.3]):

$$f \text{ x } R \approx 3 \qquad [1.3]$$

with:

– f: frequency in Hz;

– R: radius of the bubble in m.

It must be noted that this equation only gives an approximate value of the bubble resonance size. However, it is possible to estimate that a bubble with a 0.15 mm radius will resonate with an ultrasonic wave of 20 kHz.

A bubble can become unstable and collapse, often violently, in a single acoustic cycle or after a few cycles; this is called transient cavitation. Otherwise, it can oscillate for several cycles around a linear resonance size; this is known as stable cavitation.

1.2.1.1. *Stable cavitation*

At low ultrasonic intensity (1 to 3 W/cm^2) (Suslick 1989; Laugier 2007), the gas bubble responds linearly to pressure variation; its diameter varies sinusoidally simultaneously with pressure, and it oscillates about an equilibrium position for several cycles. Its oscillation amplitude is low and its lifetime is long.

1.2.1.2. *Transient cavitation*

At high ultrasonic intensity (> 10 W/cm^2) (Suslick 1989; Laugier 2007), the bubble becomes unstable, its response becomes non-linear, and after a few cycles it collapses and implodes violently in less than a microsecond. The expansion phase being isothermal and the collapse phase adiabatic, the bubble concentrates all the acoustic energy. At the time of implosion, temperatures of about 5,000 K and pressures close to 1,000 atm are observed within the bubble as well as heating and cooling rates above 1010 K/s. It undergoes asymmetric distortions and violent jets of liquid of around 100 m/s are projected into the bubble, forming new microbubbles in the liquid, leading to divergent waves in the immediate vicinity (low frequency shock waves). The life of transient cavitation bubbles is short and only determined by the ultrasonic frequency.

Abrupt variations in the medium subjected to ultrasound are characterized by an increase in temperature of the liquid medium, the formation of free radicals and high agitation. It is these very intense local physical and chemical effects at the time of implosion that are at the basis of the applications using cavitation. All these considerations are the subject of the hotspot theory. The intensity of a transient collapse can sometimes be characterized by the emission of light called sonoluminescence. The intensity of the light emitted depends on various factors (Leong *et al.* 2011) including:

– the concentration of gas dissolved in the liquid;

– the frequency of ultrasound passing through the medium;

– the amplitude of the pressure waves;

– hydrostatic pressure;

– the addition of particulate solutions.

A large number of theories have been developed on the mechanism of sonoluminescence. Numerical simulations show that the main mechanism explaining the light emission is bremsstrahlung radiation resulting from a neutral electron-atom collision in the weakly ionized plasma formed inside the heated bubble.

1.2.2. *Factors affecting cavitation*

The parameters specific to the ultrasonic wave, but also the conditions to which a reaction system is subjected, as well as the properties of the medium in which the wave propagates, can strongly influence the intensity of acoustic cavitation, which then directly affects the speed or the efficiency of the chemical reaction.

Also, the following parameters will affect the occurrence of the acoustic cavitation in a liquid medium.

1.2.2.1. *Power consumption*

This is the parameter with the greatest effect since a minimum power is required for cavitation to occur (Blake threshold). It is about

0.5 W/cm² of surface area of the vibrating source at a frequency of 20 kHz in water, and about a few W/cm² for organic solvents. The ultrasound intensity increases with the power delivered up to a limit corresponding to the formation of a shield of cavitation bubbles on the emitting surface, which strongly weakens the wave and intensity of the ultrasound.

1.2.2.2. *Frequency*

Even if all the mechanisms are not yet fully understood, it is generally admitted that in water the so-called low frequencies, ranging between 20 and 80 kHz, lead to relatively few but large transient cavitation bubbles. Thus, physical effects predominate over chemical ones. However, the so-called high frequencies, ranging between 150 and 2,000 kHz, generate many transient cavitation bubbles of smaller dimensions, thus promoting the production of hydroxyl radicals and radical oxidation reactions of hydrophilic organic solutes, for example. Indeed, the increase in frequency decreases the depth of penetration of the ultrasonic wave and also the maximum pressure reached during implosion. It is therefore necessary to increase the sound power to obtain the same effects as at low frequency.

1.2.2.3. *Pressure*

Increasing the pressure means increasing the cavitation threshold, but also intensifying the violence of bubble implosion (Neppiras 1980).

1.2.2.4. *Temperature*

As the temperature increases, the solubility of the gases in a liquid decreases and the vapor pressure of the liquid increases, lowering the cavitation threshold. As an increase in temperature reduces the effectiveness of ultrasound, an optimal temperature is observed when ultrasound is used for chemical reactions (Mason and Lorimer 1988).

1.2.2.5. *Properties of the liquid*

Three physical properties of the liquid can impact the intensity of ultrasound: vapor pressure, interfacial tension and viscosity. An increase in the vapor pressure decreases the cavitation threshold, and decreases the pressure and temperature values observed when the bubble implodes. Similarly, high interfacial tension and viscosity increase the cohesion of the liquid and thus the cavitation threshold. In addition, an increase in viscosity affects the propagation of the wave by increasing its absorption.

1.2.2.6. *Presence of dissolved gases*

The polytropic factor (γ) which depends on the nature of the gas dissolved in the liquid through which the ultrasonic wave passes impacts cavitation (McNamara *et al.* 1999). Thus, a monatomic noble gas such as argon leads to higher temperatures and higher maximum pressures than a polyatomic gas. In addition, two monoatomic gases do not behave identically; helium is less efficient than argon and xenon because of their calorific capacity values (Cp Xe = 0.158 J $K^{-1}g^{-1}$ and Cp He = 5.193 J $K^{-1}g^{-1}$, Cp Ar = 0.52 J $K^{-1}g^{-1}$). Indeed, in the presence of a gas with low heat conductivity, the temperature reached at the time of implosion is higher than in the presence of a gas with high heat conductivity. In addition, a gas with a high solubility in the irradiated medium facilitates the appearance of cavitation, as well as the presence of impurities.

1.2.2.7. *Reactor geometry*

Various studies have clearly shown the influence of the geometry of the ultrasonic reactor and the height of the irradiated liquid on the acoustic field (for example de La Rochebrochard *et al.* 2012). If a sonotrode is used, its height and position also have a clear impact on the ultrasonic field. In addition, the limits of acoustic zones depend on the diameter of the transducer and the frequency. All these parameters will determine the distribution of the wave in the reactor.

1.2.3. *Estimation of ultrasonic parameters*

The ultrasonic parameters that were considered relevant through experimentation and modeling are presented in the following section.

1.2.3.1. *Ultrasonic wave velocities in pure fluids and mixtures*

The propagation rate (C, m/s) of an ultrasonic wave in pure water at 20°C is 1,482 m/s. In general, this velocity is a function of the temperature of the medium (T in °C) and the number of carbons Cn of the fluid passed through and can be calculated in pure fluids according to equation [1.4]:

$$\mathrm{C} = \mathrm{a} + {}^{\mathrm{b}}/_{\mathrm{C_n}} - (\mathrm{d} + \mathrm{e}/\mathrm{C_n})\mathrm{T} \qquad [1.4]$$

with:

- C: propagation speed of the ultrasonic wave in m/s;
- T: medium temperature in °C;
- C_n: number of carbons of the medium crossed.

The constants of the equation were determined by Wang and Nur (1991) for linear alkanes and terminal alkenes. The authors also measured ultrasonic wave propagation rates as a function of temperature in these hydrocarbons and in naphthens using an ultrasonic pulse transmission method. The results show that the velocities of all the hydrocarbons studied decrease linearly as the temperature increases, with a different rate depending on the nature of the hydrocarbons. In addition, the speed of the ultrasonic wave increases with the number of carbons, with an intensity inversely proportional to it. Hydrocarbons in the same homologous series with a higher number of carbons have lower compressibilities.

The compression rate of an ultrasonic wave in a hydrocarbon mixture can be expressed according to equation [1.5]:

$$C_{mixture} = \sum_{i=1}^{i=n} X_i \, C_i \qquad [1.5]$$

with:

- Xi: volume fraction of the ith compound of the mixture;
- C_i: velocity of the ith compound of the mixture.

1.2.3.2. *Acoustic power*

Different methods are available in the literature to evaluate dissipated power ($P_{\mathrm{dissipated}}$) in a reaction medium. Even if a precise determination of acoustic power is fundamental, for example to enable a good reproductibilty of sonochemical reactions, there is still a lack of precision in the litterature of that matter, many papers omitting a clear description of the method they use to determine it. Some authors report ultrasonic power densities in W/cm^2 of emitting surface or ultrasonic power densities in W/m^3 of irradiated liquid but do not give any details on the measurement method used. Others only specify the electrical power indicated on the power generator, or on the wattmeter placed upstream of the installation. Finally, some rely on measurements of dissipated power evaluated by calorimetry. The latter method can be considered as the standard method used by most authors (Mason *et al.* 1992). Thus, the power can be expressed according to equation [1.6]:

$$P_{\mathrm{dissipated}} = \left({}^{dT}\!/_{dt}\right)_{t=0} mC_p \qquad [1.6]$$

with:

– Cp: heat capacity of the medium;

– m: mass of water subjected to the ultrasonic field;

– $\left({}^{dT}\!/_{dt}\right)_{t=0}$ Slope at the origin of the curve T = f(t), increase in the temperature of the liquid medium as a function of its exposure time to ultrasonic irradiation.

This equation makes it possible to calculate the ultrasonic power dissipated in W in a body of water in kg of heat capacity J.kg-1.K-1, which undergoes a temperature rise dT in K during a time dt in seconds. The increase in the initial temperature of the system is independent of the initial temperature of the medium (less than 40°C), the height of the liquid in the reactor and the size of the probe (Thompson and Doraiswamy 1999). In addition, equation [1.6] is only valid if we consider that the reactor is adiabatic and that we accept that the total power transmitted by ultrasound is transformed into heat.

This method, which is therefore not very precise and subject to many artifacts (overheating of the temperature sensor due to friction forces, heat loss at the liquid-air interface, etc.), makes it possible to estimate the conversion efficiency of the electrical power consumed into acoustic power (dissipated power). As mentioned previously, many authors do not communicate this value of dissipated power, making their work difficult to interpret, reproduce or compare.

1.2.3.3. *Ultrasonic intensity*

The maximum ultrasonic intensity (I_{max}) of a planar or spherical progressive wave is related to the pressure amplitude ($\mathcal{P}_A$) by equation [1.7]:

$$\mathrm{I_{max}} = {\mathrm{P_A^2}}/{2\rho\mathrm{C}} \qquad [1.7]$$

with:

– ρ: fluid density (kg/m^3) ;

– C: velocity of sound in the medium;

– ρC: acoustic impedance (Z) of the medium, whose value is equivalent to $1.5 \times 10^{6/}m^2/s$ in water.

The intensity (I) decreases as the distance (d_T) from the emitting source increases (equation [1.8]):

$$I = I_{max}e^{(-2\alpha d_T)} \qquad [1.8]$$

with α: attenuation coefficient of the medium.

When an ultrasonic probe is used, the intensity (I_{diss}, actual measured value) of the ultrasound on the surface of the probe is expressed in W/m^2 and then represents the sound power per unit area (equation [1.9]):

$$I_{diss} = {\mathcal{P}_{diss}}/{A_S} \qquad [1.9]$$

with A_S: probe surface area (m^2).

1.2.3.4. *Radical production*

The extreme temperature conditions generated by the collapse of the cavitation bubbles lead to the formation of radical chemical species. In water, ultrasonic waves generate radicals by the homolytic cleavage of the water molecule (equation [1.10]):

$$H_2O \longrightarrow H^{\cdot} + OH^{\cdot} \qquad [1.10]$$

The radicals formed in this reaction are very reactive and interact rapidly with other radicals and/or chemical species in solution. The radicals $H^{\cdot}$ and $OH^{\cdot}$ are commonly referred to as primary radicals; although their production and quantification can be done using different techniques, the most conventional chemical dosimeter to characterize the production of free radicals under ultrasonic irradiation is potassium iodide.

The efficiency of the molecular iodine production reaction by irradiation of an aqueous solution of potassium iodide at a given time is considered to be a relative measure of acoustic cavitation performance. This reaction, known as Weissler's (Weissler *et al.* 1950), is often used because it is easy to implement and does not require specific equipment. It consists of quantifying the species formed during the sonolysis of water into $H^{\cdot}$ and $OH^{\cdot}$ radicals, thanks to the oxidation of iodide ions to iodine by about 10% of the $OH^{\cdot}$ radicals produced and transferred in liquid phase (equation [1.11]):

$$\mathrm{OH}^{\cdot} + I^- \longrightarrow OH^- + {}^{1}\!/_{2}\, I_2 \qquad [1.11]$$

$k_1 = 1{,}1 \times 10^{10}\, L.mol^{-1}.s^{-1}$ (Motohashi and Saito 1993)

In the absence of a radical trap, hydroxyl radicals recombine in the gas phase or at the gas-liquid interface and form hydrogen peroxide (equation [1.12]):

$$OH^{\cdot} + OH^{\cdot} \longrightarrow H_2O_2 \qquad [1.12]$$

$k_2 = 6.2 \times 10^9 L.mol^{-1}.s^{-1}$ (Rabani and Matheson 1966)

The reaction of hydrogen peroxide with iodide ions leads to molecular iodine (equation [1.13]):

$$H_2O_2 + 2I^- \rightarrow 2OH^- + I_2 \qquad [1.13]$$

The molecular iodine then reacts with the excess iodide ions to form triiodide ions (equation [1.14]):

$$I_2 + I^- \rightarrow I_3^- \qquad [1.14]$$

The concentration of I_3^- is evaluated by measuring its absorbance at 355 nm ($\varepsilon = 26303$ dm^3.mol^{-1}.cm^{-1}) (Koda *et al.* 2003).

1.3. Laboratory and industrial equipment

Ultrasound is produced by mechanical, piezoelectric or magnetostrictive converters. Mechanical converters transform the circulating energy of a liquid into mechanical vibrations. Piezoelectric converters, also called transducers, deform under the effect of the electrical voltage of an alternating current that also generates mechanical vibrations. Magnetostrictive converters have comparable properties when subjected to a magnetic field from an alternating electric current. Coupled with other elements of the system, these ultrasonic frequency vibrations will propagate to the reactor containing at least one liquid phase.

The most commonly used transducers are made of piezoelectric materials and will be the only ones detailed in this chapter, as well as the devices they equip. They are made of natural or synthetic single crystals (such as quartz) or ceramics made of barium titanate or lead titano-zirconate (PZT) $Pb(ZrxTi_{1x})O_3$ which are lightweight and easily machinable. They are generally produced in the form of a disc, plate or ring on which two metallized electrodes are fixed. The material, subjected to the electrical voltage applied to the electrodes, expands or compresses according to the polarization of the ceramic. These variations are only a few micrometers and are sometimes too small to produce interesting effects in the reactor. In order to amplify the phenomenon to a few tens of micrometers, piezoelectric materials can be stacked between two metallic masses whose nature and cross-section orient the signal in a given direction.

Ceramics alone are rarely used. They are glued or flanged to a metal or glass mass (and sometimes a counter mass), thus being isolated from the reactor. The applied frequency and the geometry of the transducer obtained influence the deformation. It reaches a maximum at the resonance frequency, thus maximizing the energy conversion.

The electrical generator converts the incoming current into an alternating current with a frequency corresponding to the transducer's resonant frequency. It can be designed to deliver one or more frequencies. As each transducer is of a different design, a frequency tuning should be performed before any use when the multi-frequency generator is chosen.

The conversion of electrical energy into an acoustic one remains modest, around 40%, and is at the heart of manufacturers' concerns. The development of this technology at an industrial scale is increasing and requires constant innovation. It should be noted that the transmission of ultrasound to a liquid increases its temperature according to the intensity of the wave and the irradiation time. The units can be equipped with heating or cooling systems depending on their intended use.

The most common laboratory equipment is presented and analyzed in this section. Industrial equipment is described on the sites of manufacturers such as BPAC, Branson, Elmasonic, Hielscher, KKS, SinapTec, Synétude, etc.

1.3.1. *Ultrasonic bath*

The ultrasonic bath, with frequencies between 25 and 50 kHz (up to 120 kHz in industry) and volumes ranging from less than one liter to several m^3, is the most widespread piece of equipment in laboratories, especially in industry. It is used for cleaning, emulsification, dispersion of solids in a liquid medium, extraction, degassing and the implementation of reactions involving “fragile” substances such as cells and enzymes. Indeed, the ultrasonic energy dissipated in the bath is around 1 to 5 W/cm^2 of emitting surface. Transducers are usually placed under the bottom of the bath, sometimes lining the walls to ensure maximum coverage of the tank. They usually deliver only one frequency, but multi-frequency systems are also available on the market (Figure 1.13).

The bath is usually filled with water or another liquid (containing a detergent if required). When it comes to cleaning machining pieces, for example, the bath is the ultrasonic reactor in which they are immersed. In the case of a reactor immersed in the coupling liquid, ultrasonic irradiation is indirect. The liquid level is therefore important. For a better energy conversion, it will be adjusted according to the emission frequency (λ = 75 mm at 40 kHz). The acoustic field depends on the position of the transducers and it is not homogeneous. It is therefore advisable to identify the most intense areas marked by the deformation of the liquid on the surface, and to place the parts or reactors there. Flat-bottomed reactors are preferable to round-bottomed ones because the latter transmit waves less efficiently (Kardos and Luche 2001). Ultrasonic baths can be equipped with heating systems or cooling coils.

Baths are often used to test a new reaction, but reproducibility remains limited due to adjustment parameters (liquid level, position in the tank, inhomogeneity of the ultrasonic field in the bath, temperature, indirect irradiation, etc.).

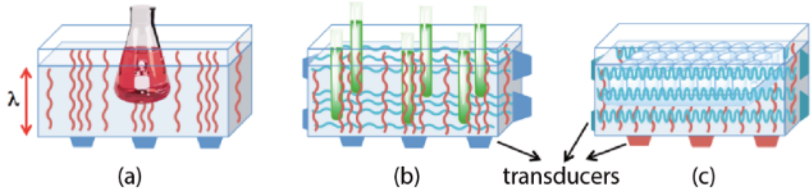
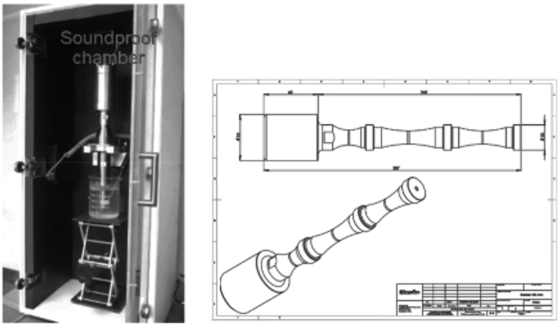


Figure 1.13. *Different ultrasonic baths: (a) single-frequency bath; (b) single-frequency tank with orthogonal transducers; (c) multi-frequency bath. For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*

1.3.2. *Ultrasonic probes*

The ultrasonic probe, usually made of titanium alloy, allows direct irradiation of the medium at higher acoustic powers than the bath. This system is used to homogenize and break cells, and for any reaction that requires efficient and strong stirring. It consists of a transducer, a counterweight called an amplification probe and the removable part. The counterweight increases the amplitude of the ultrasonic wave. The removable probe, of variable length and diameter, transmits ultrasound to the reaction medium in which it is immersed. The volumes considered are from a few milliliters to several liters. The length of the probe is defined and corresponds to half a wavelength (12.5 cm at 20 kHz). The intensity of the wave is inversely proportional to the emitting surface. Over time, the latter undergoes erosion due to cavitation, which should be minimized by flattening the tip by very light sanding after two or three uses. However, it is important to avoid a significant loss that leads to a discrepancy between the probe and the frequency generator, leading to a “silent” device. Radial emission probes provide a more homogeneous distribution of the wave in the liquid to overcome this disadvantage (Figure 1.14). Generators can deliver a continuous or pulsed wave, in order to better control the temperature of the irradiated medium. Low-frequency ultrasonic reactors cause audible waves to be scattered and can then be placed in a transparent wall acoustic box to reduce noise pollution.



(a) (b)

Figure 1.14. *Ultrasonic probes (source: with the kind permission of SinapTec): (a) 20 kHz probe with acoustic box; (b) 20 kHz radial probe*

1.3.3. *High frequency reactors*

High-frequency reactors are mainly used in research laboratories in work that most often requires the pyrolysis of molecules or the production of oxidizing free radicals such as $OH^{\cdot}$. They are designed according to the tank principle: a piezoelectric ceramic, of calibrated thickness ($n/2 \times \lambda$, $n = 1$ to 3) corresponding to the desired frequency, is glued to a borosilicate or quartz glass window forming the bottom of the reactor. This is a double jacketed tank equipped with a cooling system (Figure 1.15). The irradiation of the medium is considered direct and propagates from the bottom to the top. The optimal frequency adjustment is determined by the height of a small geyser of misty liquid on the surface of the reaction medium. In order to guarantee long-term use of the ceramic, it is cooled by an air current during each experiment. Overheating could lead to the total deactivation of the material when reaching its Curie point.

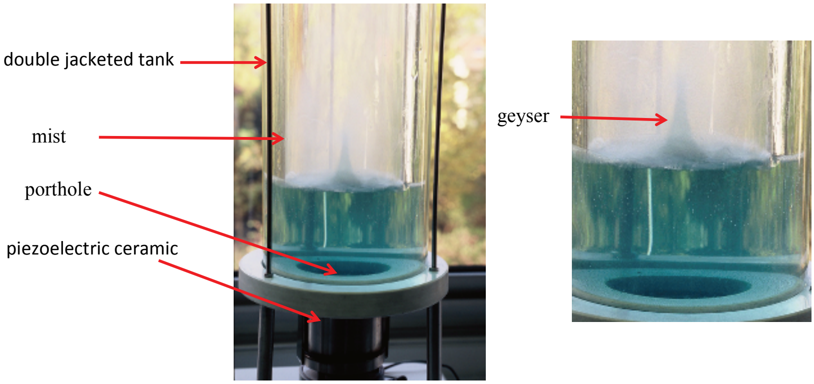


Figure 1.15. *High frequency reactor. For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*

1.3.4. *Cup-horn reactors*

Cup-horn reactors are similar to high-power ultrasonic tanks. However, they do not have the disadvantages of the latter. They are designed like high-frequency reactors, with the probe at the bottom of the reactor in direct contact with water (general case)

(Figure 1.16). The reaction parameters are thus better controlled: homogeneity of the ultrasonic field and temperature. Small borosilicate glass containers are immersed in this "bath", such as erlenmeyers, beakers or test tubes.

Figure 1.16. *Cup-horn reactor. For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*

1.3.5. *Continuous reactors*

Continuous reactors allow the treatment of larger volumes by circulating the reaction medium in an open system subjected to the ultrasonic field. They can be of variable geometry, the tubular shape being one of the most commonly used (Figure 1.17).

Figure 1.17. *Continuous reactor (source: courtesy of SinapTec)*

1.4. Green organic sonochemistry

For many years, the sonochemistry of solutions has only found limited interest in the eyes of chemists. Until the 1980s, ultrasound was only very rarely used by organic chemists (for example, Luche and Damiano 1980). Although cavitation caused by an ultrasonic wave is an extremely effective and versatile tool for carrying out organic chemistry reactions, the effects were not well-known. Thus, it is by explaining these different effects that the reactions have been classified into three distinct categories, also called “types”, of sonochemical reactions giving rise to what Jean-Louis Luche described as true or false sonochemistry (Luche *et al.* 1990).

1.4.1. *True and false sonochemistry*

1.4.1.1. *True sonochemistry*

Type I reactions: these homogeneous phase reactions occur near a cavitation bubble at the time of its implosion. They thus benefit from the extreme temperature and pressure conditions that prevail there and which generate very reactive free radicals that can affect the reaction: this is the hotspot theory. It is thus considered that the effect of ultrasound is chemical since cavitation influences the reaction mechanism.

Type III reactions: these reactions in the heterogeneous phase generate mono-electronic transfers and are deemed ambivalent because they benefit from the chemical effects but also from the physical effects of ultrasound; it is nevertheless difficult to determine the real effect of the latter.

1.4.1.2. *False sonochemistry*

Type II reactions: these heterogeneous phase reactions only benefit from the physical effects of microemulsion ultrasound, improved mass and heat transfer, degassing, particle size reduction, etc. No changes in the reaction mechanism due to cavitation, from which the chemical intermediates are not derived, are observed. These reactions, although described as “false sonochemistry”, are nevertheless extremely valuable.

1.4.2. *Synthesis in a homogeneous and heterogeneous system*

1.4.2.1. *Synthesis in a homogeneous system*

Even if a system composed of a homogeneous liquid in which bubbles are generated cannot be considered strictly homogeneous, in sonochemistry, it is the state of the system before ultrasonic irradiation that is considered. Sonochemical syntheses under homogeneous conditions are rarely described in the literature because they are often difficult to interpret. However, the reported studies show that sonochemical effects occur at the time of cavitation bubble collapse, inside the bubble where conditions are extreme, at the cavitation-liquid bubble interface where conditions are less extreme, and in the liquid where mechanical effects predominate (Figure 1.18).

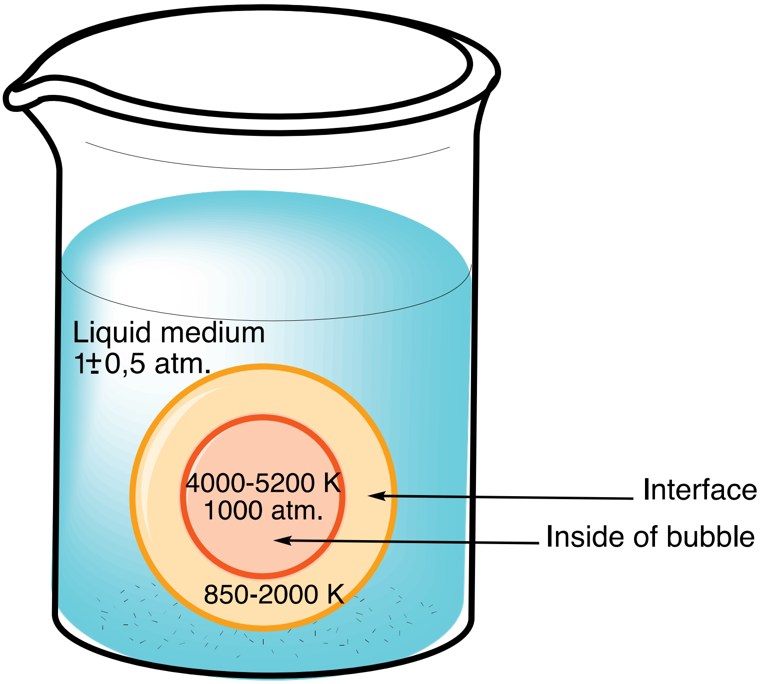


Figure 1.18. *Chemical reaction sites in an aqueous medium subjected to acoustic cavitation according to the "hotspot" theory*

1.4.2.2. *Reactions in the gas phase, inside the bubble*

For a chemical compound to be submitted to the extreme conditions generated inside the cavitation bubble at the time of its collapse, it must be easily driven out of the solution, both because of its low solubility in the solution and/or its relatively high volatility compared to the solvent (Luche 1998). Pyrolysis reactions and homolytic rupture of water occur in the gas phase.

1.4.2.2.1. Aqueous systems

In water and aqueous solutions, the predominant phenomenon is the sonolysis of the water, which occurs in the gas phase of the bubble. The oxidizing species formed can react with the co-vaporized organic compounds.

1.4.2.2.2. Organic systems

For many years, pure organic fluids have been considered much less sensitive to sonolysis than water, due to lower cavitation energies. However, extreme conditions are also observed in organic fluids and no solvent escapes sonolysis.

1.4.3. *Synthesis in a heterogeneous system*

The use of ultrasound, particularly low-frequency ultrasound, appears to be a method of choice to overcome the constraints inherent in multiphase systems. The use of ultrasound is thus described for many such reactions. Two of the three categories in which Jean-Louis Luche has rationalized sonochemical reactions concern heterogeneous media (Luche 1993): heterogeneous “type II” reactions that take advantage of the mechanical effects of ultrasound and “type III” reactions that couple these physical effects to radical chemistry phenomena that can be induced by ultrasonic irradiation. This double impact sometimes makes it difficult to interpret the real effects of ultrasound for this type of system and many authors simply note the influence of ultrasound on reaction yields without giving precise explanations.

When an ultrasonic wave passes through a heterogeneous system, the physical effects induced are mainly of two kinds depending on the nature of the medium.

1.4.3.1. *Physical effects at liquid/liquid interfaces*

In the case of liquid/liquid biphasic systems, sonication causes an intense microemulsion phenomena. When the cavitation bubble forms near the liquid/liquid interface, a deformation of the bubble is observed relative to the spherical model leading to the formation of “microjets” of liquid that can be projected from one phase to another at several hundred meters per second. This microemulsion phenomenon causes the propulsion of microdroplets from one phase to another and ensures significant contact between the reagents present in each of the immiscible phases. Emulsions of this type are finer and more stable than those obtained in a conventional way. As a result of this efficient material transfer, ultrasound is often defined as a physical phase transfer agent.

1.4.3.2. *Physical effects at liquid/solid interfaces*

In the case of liquid/solid biphasic systems, the main physical effect induced by ultrasound comes from the reduction in the size of the solid particles. At a solid surface, the effect of the "microjet" depends on the ratio d/R, where d represents the distance between the bubble and the solid and R the radius of the bubble. When this ratio is less than 0.3, the velocity of the jet is estimated at 200 $m.s^{-1}$ and the erosion of the solid is then at its maximum (Lauterborn and Ohl 1997). Cracks form in the solid and fine particles are then ejected into the medium, causing an increase in the specific surface area of the solid. This results in better contact between the reagents in the liquid phase and the solid product, thereby improving the effectiveness of the reaction.

The following section provides relevant examples of the use of ultrasound, as an unconventional activation technique, for organic synthesis.

1.4.3.3. *Organic sonochemistry: ultrasound, an unconventional activation technique*

1.4.3.3.1. Elimination reactions

Different elimination reactions such as dehalogenation reactions can be performed under ultrasound. For example, Diez-Barra and collaborators proposed a solvent-free β-elimination reaction of β-bromoacetals in the presence of a base and under ultrasound (Diez-Barra *et al.* 1992) (Figure 1.19).

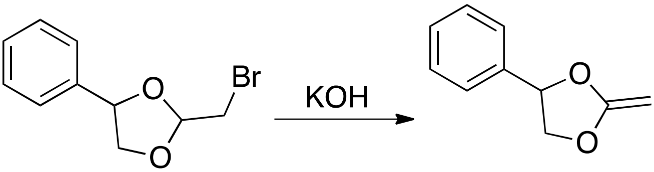


Figure 1.19. *β-elimination of β-bromoacetals in heterogeneous media (adapted from Diez-Barra* et al. *1992)*

In this heterogeneous reaction, sonochemical activation leads to yields equivalent to those obtained with a phase transfer agent, thus demonstrating the importance of the physical effects of ultrasound. The results of this study are presented in Table 1.1.

Activation	Temperature (°C)	Time (min)	Yield (%)
None of them	90	90	37
Phase transfer agent	90	90	68
Ultrasounds	75	60	65

Table 1.1. *Yield of the β-elimination reaction of β-bromoacetals under various experimental conditions (adapted from Diez-Barra* et al. *1992)*

1.4.3.3.2. Substitution reactions

The study of ultrasound-assisted substitution reactions is relatively old and has, for example, been described by Luche *et al.* for Bouveault aldehyde synthesis (Pétrier *et al.* 1982). Represented in Figure 1.20, it consists in the transformation of an allyl halide into an aldehyde.

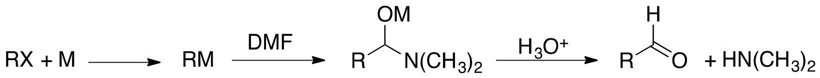


Figure 1.20. *Ultrasound-assisted Bouveault reaction (adapted from Pétrier* et al. *1982)*

In this study, the use of ultrasound results in much higher yields, and fewer by-products, than with conventional processes. A physical effect of ultrasound on metal surfaces, involving an increase in the specific surface area of the latter, is suspected here.

In solid/liquid biphasic systems, ultrasound has been used for aromatic electrophilic substitution reactions such as Friedel–Crafts reactions (Yadav and Majeebur 2003). As part of this electrophilic substitution, the authors used acid catalysts such as amberlyst 36. The use of a catalyst and the absence of a radical mechanism for the reaction tend to prove that the chemical effects are again disadvantaged. The same type of phenomenon can be observed for the acylation of pyrrole catalyzed by Hβ-zeolites modified with phosphoric acid (Bai *et al.* 2012).

Rajanna and her collaborators have also described a Friedel–Crafts acylation reaction using an acetamide/SO_2Cl_2 mixture as a reagent (Satish Kumar *et al.* 2014). This study compares microwave or ultrasonic activation methods with traditional synthesis pathways; in both cases, a significant decrease in reaction time is observed for reactions under ultrasound (from 4–6 hours to 30–40 minutes) and under microwave (from 4–6 hours to 3–4 minutes).

Although little information on experimental protocols is provided, the homogeneity of the medium does not eliminate the benefit of micro-mixing due to the physical effects of ultrasound, while the chemical effects of ultrasound do not seem to play a major role; indeed, the reaction mechanism does not involve radicals. It is then possible that the acceleration of the reaction is simply due to the warming up of the medium during sonication. This warming up effect – useful when measuring acoustic power by calorimetry – must be imperatively controlled, for example by a cooling system via a double jacketed reactor, in order to evaluate the real effect of ultrasound on the chemical reaction. In the case of this study, as in many other publications, the absence of strict and detailed control of operating conditions prevents any rationalization of the results obtained and it seems difficult to even affirm that ultrasound has a beneficial effect on the reaction.

Friedel–Crafts acylation reactions have been performed where the effect of sonication is clearer and more explicable. Bai *et al.* (2012) describe, for example, the acylation reaction of pyrroles in a heterogeneous system. This reaction is catalyzed by Hβ-zeolites modified with phosphoric acid. The heterogeneity of the catalyst can in this case take advantage of the phenomenon of particle size reduction induced by ultrasound.

In the case of heterogeneous liquid/liquid reactions, Fujita and colleagues (Fujita *et al.* 2015) proposed a process for ultrasound-assisted bromination of aromatics in a heterogeneous water/carbon tetrachloride medium. The reaction in this heterogeneous liquid/liquid medium is shown in Figure 1.21.

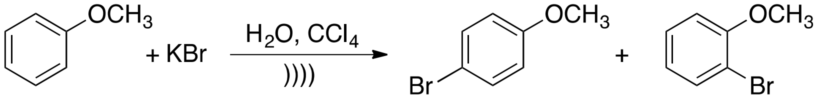


Figure 1.21. *Ultrasound-assisted bromination reaction of anisole (adapted from Fujita* et al. *2015)*

For this reaction, low-frequency (36.6 kHz) and high-frequency (480 kHz) ultrasound irradiations were tested and a significant effect of frequency on reaction kinetics was observed, for example for bromoanisole. As frequency strongly influences reaction kinetics and given the absence of reaction without irradiation, this clearly indicates a chemical effect of ultrasound. The authors propose a radical mechanism based on the decomposition of carbon tetrachloride in the presence of water (Kimura *et al.* 1996). The compounds thus formed react in turn with the bromide ions to produce bromination of the aromatic compound. Since this reaction requires the use of CCl_4, we can nevertheless question the legitimacy of its “green” nature.

1.4.3.3.3. Condensation reaction

Condensation reactions are intrinsically attractive from the point of view of green chemistry because they generally allow good results to be obtained in terms of atom economy. It is therefore interesting to carry out these reactions using a so-called sustainable activation source such as ultrasound. A Claisen–Schmidt condensation reaction assisted by ultrasound has been studied to obtain chalcones in order to develop antibacterial agents (Calvino *et al.* 2006). For this study, basic activated carbons (Na and Cs-Norit), favorable from the point of view of green chemistry, were used as heterogeneous catalysts. Figure 1.22 describes the type of reaction performed.

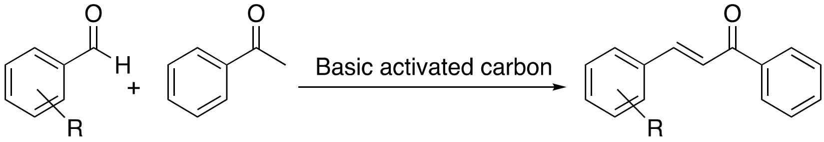


Figure 1.22. *Condensation reaction between a benzaldehyde and acetophenone (adapted from Calvino* et al. *2006)*

Ultrasound-assisted reactions are performed at relatively low frequencies, promoting the physical effects of ultrasound, thereby reducing the size of the activated carbon particles and thus increasing their specific surface area.

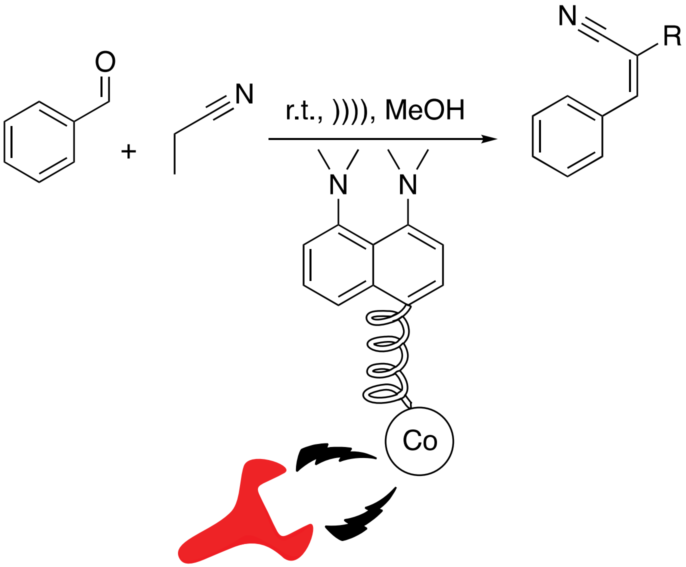


Figure 1.23. *Ultrasound-assisted reaction of Knoevenagel between benzaldehyde and a nitrile (adapted from Schneider* et al. *2014)*

An original sonochemical process has been developed for the reactions of Knoevenagel and Claisen–Schmidt. In this case, the catalyst (1,8-bis (dimethylamino)naphthalene or *proton sponge*) is grafted onto nanomagnets to facilitate the processing phase of the reaction. Figure 1.23 clearly summarizes the principle of this process for which the catalyst can be easily recovered by magnetism (Schneider *et al.* 2014).

In this study, an increase in the reaction rate is observed when the medium is subjected to ultrasonic irradiation. Stark *et al.* demonstrated this effect for the reaction between benzaldehyde and malonitrile (Schneider *et al.* 2014).

In addition, low-frequency ultrasound (ultrasound bath) allows a good dispersion of the catalysts in the solution. The use of this type of equipment has the disadvantage of generating repeatability problems because of the inhomogeneity of the ultrasonic field in the tank.

The condensation reaction of benzoin was also studied under low-frequency ultrasonic irradiation (ultrasonic probe, f = 20 kHz) (Estager *et al.* 2007). This polarity reversal reaction or "umpolung" allows the condensation of two benzaldehyde molecules into one benzoin molecule. In this study, different ionic liquids with dialkylimidazolium cations were used as reaction catalysts, acting as a platform for polarity reversal via carbene formation (Figure 1.24).

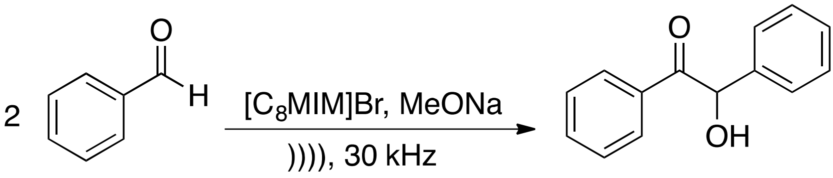


Figure 1.24. *Ultrasonic benzoin condensation reaction catalyzed by octylmethylimidazolium bromide (adapted from Estager* et al. *2007a)*

The results obtained show that a physical effect of ultrasound is likely. During the reaction, the formation of solids is observed, so ultrasound prevents the formation of agglomerates that can potentially trap reagents or catalysts.

1.4.3.3.4. Oxidation reactions

Oxidation reactions are particularly popular in sonochemistry in homogeneous systems because they are performed via radical mechanisms. They are generally carried out at a high frequency and in a homogeneous aqueous medium, for example for the degradation of organic micropollutants (Serna-Galvis *et al.* 2016).

Many examples also describe heterogeneous oxidation reactions. In this case, it is often difficult to define the actual effect of ultrasound and to know whether the physical or chemical effects of ultrasound are predominant or whether it is a type III reaction coupling the two phenomena.

Oxygen, trapped by radicals resulting from the decomposition of di-tert-butylperoxide, under direct ultrasonic activation at 30 kHz in water, indirectly leads to pervaleric acid from valeraldehyde (Neuenschwander *et al.* 2012). The reaction of these two compounds then produces valeric acid. Without acoustic cavitation, this radical chain oxidation does not take place.

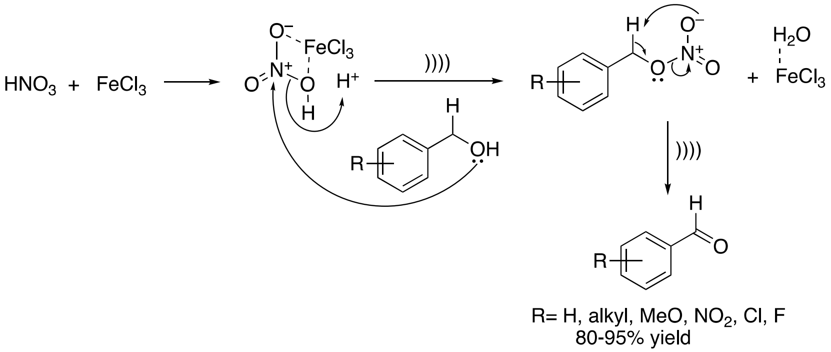


Figure 1.25. *Proposed mechanism for the ultrasound-assisted oxidation of primary benzyl alcohols using HNO^3 catalyzed by $FeCl^3$ (adapted from Naik* et al. *2011)*

The authors propose a mechanism for the oxidation, in the presence of $HNO_3/FeCl_3$, of various primary benzyl alcohols to the corresponding benzaldehydes that are more selective under ultrasonic conditions rather than under silent conditions (Figure 1.25) (Naik *et al.* 2011). Indeed, the reaction carried out in a 35 kHz ultrasonic bath leads to benzyl aldehydes in 10 to 20 minutes at room temperature without the formation of oxidation by-products.

Lee, Shaabani and their collaborators described the oxidation reaction of alkylarenes with potassium permanganate supported on K10 montmorillonite (Shaabani *et al.* 2002). Different reactions were studied, under thermal activation, microwave or ultrasound, and are described in Figure 1.26.

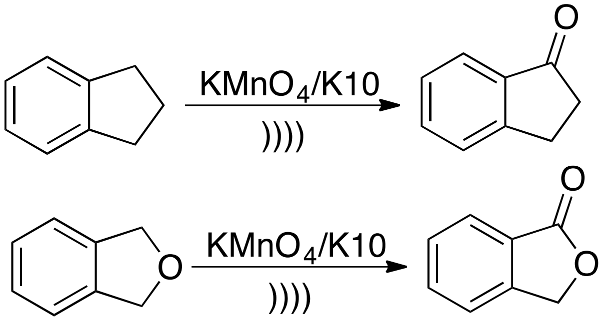


Figure 1.26. *Example of an ultrasound-assisted oxidation reaction with supported potassium permanganate (adapted from Shaabani* et al. *2002)*

Although ultrasound seems to significantly accelerate the reaction, the lack of detail on the protocol used (type of equipment, acoustic frequency and power) does not allow conclusions to be drawn about the actual effect of ultrasound. As mentioned above, it is essential to accurately describe any sonochemical process in order to be able not only to understand it but also to reproduce it.

In biphasic processes, it is often necessary to introduce a phase transfer catalyst despite the increase in the contact surface by ultrasound. This is the case when preparing benzaldehyde in an aqueous medium containing H_2O_2 and $H_3PW_{12}O_{40}$ acid as catalyst. Aliquat-336 is added to assist in the transfer of the oxidant into the chlorinated organic phase containing benzyl alcohol. A thorough study of all parameters shows that the best results are obtained with the 22 kHz ultrasonic bath (Mahamuni *et al.* 2006).

A comparable process has been developed for the oxidation of cyclanols (C5 to C8) to corresponding ketones, this time in the presence of tungstic acid H_2WO_4 (Chatel *et al.* 2014b). Although the reaction no longer requires an organic solvent, Aliquat-336 remains essential. Cyclohexanone is obtained quantitatively in 15 minutes by direct irradiation of the mixture with a 20 kHz probe.

During the study of the oxidative depolymerization of lignin, recyclable waste from the paper industry, with hydrogen peroxide in the presence of metal catalysts such as sodium tungstate, Draye, Andrioletti and their collaborators studied the effect of ultrasound (Napoly *et al.* 2015).

The different phenolic monomers resulting from the depolymerization reaction are shown in Figure 1.27.

At a frequency of 20 kHz and an acoustic power in water of 3.8 W, ultrasound does not promote the depolymerization of lignin but rather the recombination of compounds resulting from depolymerization.

The use of an ultra-turrax® disperser then allows the authors to show that the decrease in ultrasonic depolymerization yields is not due to better mass transfer but to the chemical effects induced by ultrasonic activation.

However, ultrasound is advantageous in the pre-treatment or extraction of lignocellulosic biomass (Chatel *et al.* 2014a).

This green oxidant, aqueous H_2O_2 that releases only water at the end of the reaction, is used in organic micropollutant treatment processes together with iron sulphate, Fe_2SO_4. However, this Fenton reagent has been successfully used for the regiospecific oxidation of D-glucose to D-gluconic acid, without prior protection of other hydroxyl groups (Rinsant *et al.* 2014). This result is due to ultrasonic activation, which allows the transformation to be carried out very quickly under extremely mild conditions. This study illustrates well the possible new developments in green chemistry, in the context of biomass recovery.

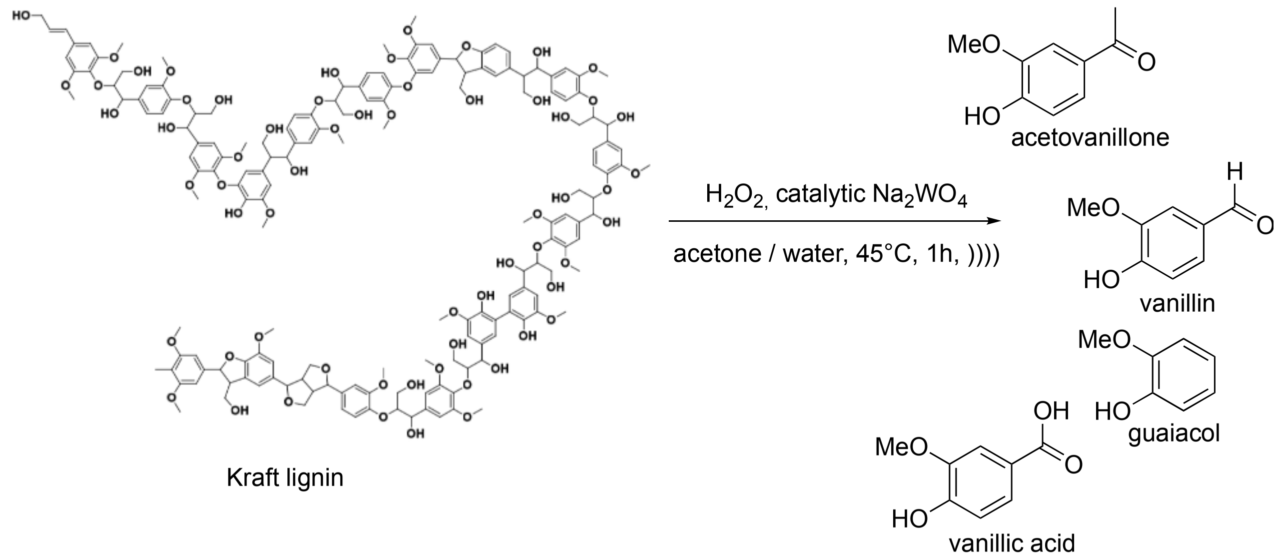


Figure 1.27. *Oxidative depolymerization reaction of lignin (adapted from Napoly* et al. *2015)*

Epoxidation reactions have also been studied in the presence of oxidants that are less harmful to the environment. The association of H_2O_2 with urea (UHP) makes it possible to epoxidize activated or deactivated chalcones into epoxyketones (Figure 1.28) (Jin *et al.* 2009). The easy-to-use ultrasonic-oxidant combination makes the process green. At 40 kHz and room temperature, yields are very high.

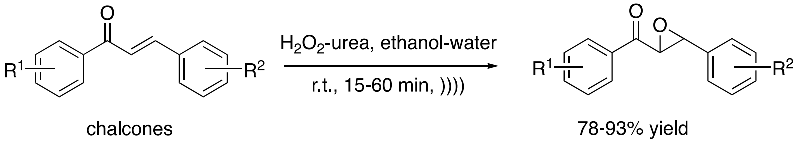


Figure 1.28. *Epoxidation of chalcones under ultrasonic activation (adapted from Jin* et al. *2009)*

Strategies have evolved towards biomimetic syntheses involving organometallic complexes of porphyrins. When iron complexes are grafted onto carbon nanotubes, the epoxidation of alkenes outweighs their oxidation into aldehydes (Rayati and Sheybanifard 2015). Ultrasound activates H_2O_2 allowing a better conversion in minimal time. The supported catalyst can be reused four times without any loss of activity.

Power ultrasound has also been used in heterogeneous ionic liquid/H_2O_2 media (Chatel *et al.* 2012a). This coupling between two green chemistry tools (ultrasound/ionic liquids) will be detailed later in this chapter. In this example, the catalyst is a Manganese complex, Mn(TPP)OAc as shown in Figure 1.29.

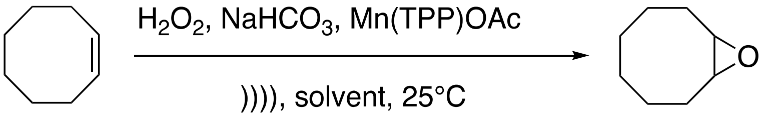


Figure 1.29. *Epoxidation reaction of cyclooctene under ultrasonic irradiation (adapted from Chatel* et al. *2012a)*

In this study, the authors propose a mechanism that involves a porphyrin-oxo-manganese complex and not bicarbonate-activated H_2O_2. In this context, the catalyst is immobilized in the hydrophobic ionic liquid and can be recycled and reused. In addition, the use of a chiral porphyrin leads to chiral epoxides with modest but promising results (Chatel *et al.* 2012b).

Sonocatalyzed oxidation allows the use of oxidizing systems that are more environmentally friendly in terms of pollution, waste reduction and of course selectivity, or even enantioselectivity. They are an interesting source of future research and development work that can be transposed to an industrial scale.

1.4.3.3.5. Reduction reactions

Although less frequent than oxidation reactions, different studies describe ultrasound-assisted reduction reactions. Song *et al.* (Peng *et al.* 2005) describe the reduction of benzophenone to alcohol by using an ultrasonic probe at a frequency of 20 kHz (Figure 1.30).

This reaction is catalyzed by zinc introduced in powder form and kept in suspension. The use of low frequency ultrasound maintains this suspension while reducing the size of the zinc particles, thereby increasing the specific surface area of this catalyst.

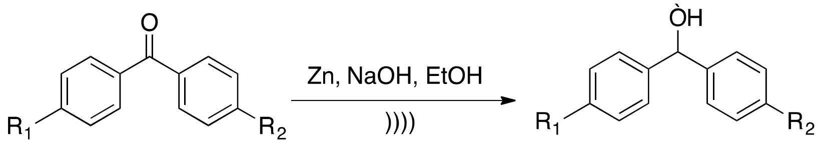


Figure 1.30. *Reduction reaction of benzophenone under ultrasonic irradiation (adapted from Peng* et al. *2005)*

Pasha and Jayashankara described the reduction of nitro-aryl to aryl amine again using a metal catalyst, aluminum (Pasha and Jayashankara 2005) (Figure 1.31).

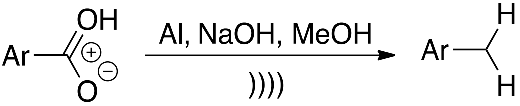


Figure 1.31. *Ultrasound-assisted reduction reaction of nitro-aryls to amino-aryls (adapted from Pasha and Jayashankara 2005)*

Various examples of double bond reduction under ultrasonic irradiation are also present in the literature, such as the selective reduction of the α,β-unsaturated ketone double bond (Wang *et al.* 1999) (Figure 1.32).

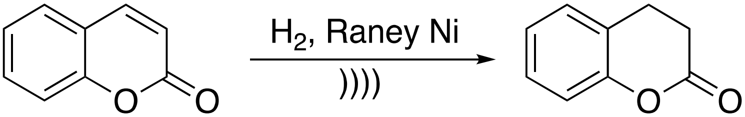


Figure 1.32. *Example of reduction of double bond under ultrasonic irradiation (adapted from Wang* et al. *1999)*

In this hydrogenation reaction, the physical effects of ultrasound on Raney nickel are probably the most significant.

Ultrasound has also been shown to be effective in reducing aliphatic nitro compounds with hydrogen produced *in situ* by a hypophosphite/hypophosphorous acid mixture in the presence of palladium on charcoal (Figure 1.33) (Letort *et al.* 2017).

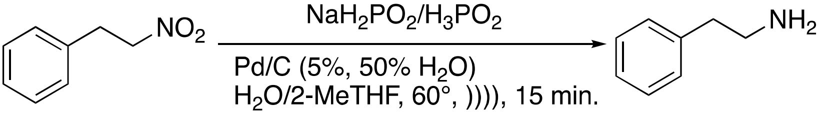


Figure 1.33. *Reduction of (2-nitro)ethylbenzene to 2-phenylethan-1-amine (adapted from Letort* et al. *2017)*

In a H_2O/2-MeTHF mixture, 90 minutes of reaction are required under silent conditions, whereas 15 minutes are sufficient under ultrasonic activation to obtain a total conversion and 90% efficiency.

However, under ultrasound at 70°C, and in water, the reaction is quantitative. The authors explain these good results by an improvement in mass transfer by ultrasound, which replaces a chemical phase transfer catalyst.

1.4.3.3.6. Cyclization reactions

The synthesis of cyclic molecules, and in particular heterocyclic molecules, is of particular interest due to their biological properties. There are also many examples in the literature. Zhang *et al.* described the ultrasound-assisted synthesis of pyrroles catalyzed by zirconium chloride (IV) (Figure 1.34) (Zhang *et al.* 2008).

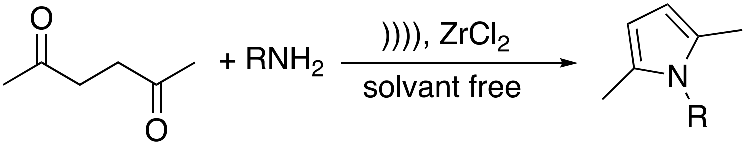


Figure 1.34. *Synthesis of pyrrole under ultrasonic irradiation (adapted from Zhang* et al. *2008)*

Although not detailed in the publication, the absence of solvent probably results in a lower solubility of zirconium salt in the medium. The physical effects of ultrasound can therefore have a relatively large effect leading to an improvement in response.

The synthesis of 1,2,3-triazole was carried out by heterogeneous catalysis in the presence of zeolites supported on bimetallic oxides (Safa and Mousazadeh) (Figure 1.35).

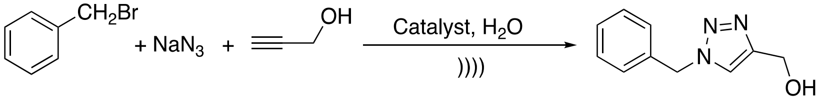


Figure 1.35. *Ultrasound-assisted synthesis of 1,2,3-triazoles in the presence of zeolites supported on bimetallic oxides (adapted from Safa and Mousazadeh)*

This click chemistry reaction was performed under irradiation with an ultrasonic probe at frequencies between 50–100 kHz. Again, the proposed non-radical mechanism and the presence of solid particles indicate a process that benefits from the physical effects of ultrasound and in particular from the reduction in particle size of the supported catalysts. It is also important to note that ultrasound, an energy technology that generates hotspots, is used here with potentially explosive compounds.

Mahdavinia and colleagues (Mahdavinia *et al.* 2009) used a hydrogen phosphate salt for the condensation of two naphthols with an aldehyde (Figure 1.36).

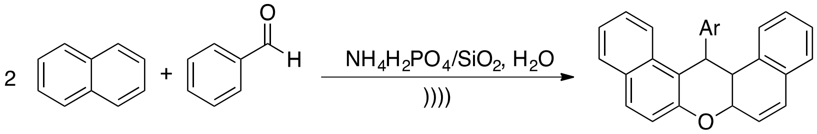


Figure 1.36. *Ultrasound-assisted condensation reaction between naphthols and aldehyde (adapted from Mahdavinia* et al. *2009)*

During this reaction in the aqueous phase, the use of ultrasound at a frequency of 25 kHz results in a very significant increase in reaction efficiency in a significantly reduced time (Table 1.2).

	Ultrasound		Silent conditions	
Catalyst (mg)	Time (min)	Yield (%)	Time (min)	Yield (%)
0	80	0	180	0
10	60	8	180	5
20	60	25	180	10
50	60	60	180	10
100	40	92	120	20
200	40	92	120	20

Table 1.2. *Synthetic yield of 14-(4-bromophenyl)-14-H-dibenzo[a,j]xanthene with or without ultrasonic irradiation (25 kHz) (adapted from Mahdavinia* et al. *2009)*

For the same reasons as in the previous example, the effect of ultrasound probably lies in its ability to reduce the size of catalyst particles but also in its ability to increase the contact surfaces between the different liquid phases (via microemulsion) resulting from the low solubility of β-naphthol in water.

1.5. Sonochemistry in unconventional environments

1.5.1. *Physical activator*

The effects induced by ultrasound on a chemical system effectively place it within the framework of green chemistry. In organic sonochemistry, for example, the chemical and/or physical effects of ultrasound can reduce the amount of additives required to ensure a smooth reaction, thus improving its environmental footprint.

In type I reactions, the use of ultrasound generates radical active species. Radicals are often generated by a radical initiator added to the reaction medium. These radical initiators are generally quite unstable and may, as in the case of some peroxides, require special storage conditions. The use of ultrasound then makes the process more eco-responsible (use of fewer chemicals), thus meeting different principles of green chemistry (Anastas and Warner 1998). Ultrasound can thus be assimilated to “physical catalysts/initiators”.

In heterogeneous type II reactions, the physical effects of ultrasound can lead to a significant increase in efficiency, either through microemulsion phenomena (in the case of heterogeneous liquid/liquid mixtures) or by reducing particle size (liquid/solid mixtures). This increase in yield without the addition of new chemical compounds alone reduces the E-Factor of the reaction (Sheldon 1994) and therefore its environmental footprint. In the case of liquid/liquid mixtures, ultrasound avoids the use of phase transfer agents (Makosza 1975) by creating a larger contact surface between the two phases. Ultrasound can be considered as “physical phase transfer agents” in heterogeneous liquid/liquid type II reactions.

Since type III reactions are a combination of type I and type II reactions (heterogeneous but with a radical mechanism initiated by ultrasound), they benefit from both the chemical and physical effects of ultrasound from a sustainable development chemistry perspective.

1.5.2. *Solvent-free chemistry*

The use of solvents is, by its very essence, contrary to the concept of green chemistry because they are often used in very large excess and are volatile. However, they remain essential in many reactions where, for example, their polar/apolar or protic/aprotic nature can play an important role or they can act as a heat buffer, helping to dissipate the energy generated by the reaction. One of the other advantages of their use is their solubility, which allows them to solubilize in a single phase different compounds that would otherwise be immiscible.

In the presence of immiscible compounds, the use of ultrasound can break down the heterogeneity of the mixture via the phenomena of microemulsion or mass transfers that they induce. There is therefore a clear synergy in this case between ultrasound and solvent-free chemistry.

Various articles describe ultrasonic and solvent-free synthesis reactions such as the Michael reaction between a secondary amine and a ferrocenylenone (Yang *et al.* 2005), biocatalysis synthesis of isoamyl butyrate (Bansode and Rathod 2014) or 3-arylcoumarin synthesis (Wetosot *et al.* 2016) (Figure 1.37).

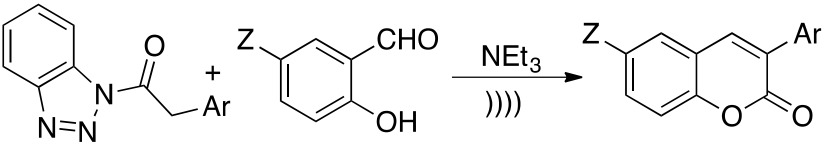


Figure 1.37. *Example of solvent-free ultrasonic synthesis of arylcoumarin under ultrasound (adapted from Wetosot* et al. *2016)*

Although the contribution of organic sonochemistry to solvent-free chemistry is undeniable, it is nevertheless important to be cautious when reacting solvent-free organic sonochemistry and to have a good knowledge of the reaction under study. Indeed, the use of solvents not only solubilizes the reagents but also the reaction products. It must therefore be ensured that the reaction mixture does not precipitate during the reaction following the formation of the product because the precipitation of the medium can lead to significant overheating of the system as well as the destruction of the ultrasonic transmitter (probe, ceramic).

1.5.3. *Ionic liquids and ultrasound*

Ionic liquids are salts composed only of ions and are, by definition, liquid at temperatures below 100°C (Hagiwara and Ito 2000). They are generally composed of an organic cation and an organic or inorganic anion and can be, in different cases, liquid at room temperature. The wide variety of ionic liquids available, sometimes estimated at 1 million simple ionic liquids, makes it possible to select an ionic liquid specifically for a given application. They are therefore sometimes referred to as *solvent designers* and can be used in a wide range of applications as diverse as catalysis (Hallett and Welton 2011), gas purification (Brennecke and Gurkan 2010; Abai *et al.* 2015), inorganic material synthesis (Freudenmann *et al.* 2011) or extraction, for example of biosourced molecules (Passos *et al.* 2014). Figure 1.38 shows the ionic liquids commonly used in the literature.

One of the most interesting properties of these liquid salts is related to their very low vapor pressure. This specific point can create a synergy with the use of sonochemistry because it can reduce or avoid nebulization phenomena as well as the tendency of solvent cavitation (Flanningan *et al.* 2005).

In many cases, the synthesis of ionic liquids is carried out in two steps, namely the reaction of a Lewis base (most often a tertiary amine) with an alkane halide by a nucleophilic substitution reaction SN2, the Menschutkin reaction when it is an amine (Menschutkin 1890), followed by an anion metathesis. Studies in the literature describe the use of ultrasound for the synthesis of ionic liquids and in particular for the anion metathesis stage (Lévêque *et al.* 2002). In this case, the solvent used, acetone, promotes phase separation that can be overcome by the effects of ultrasound-induced microemulsions.

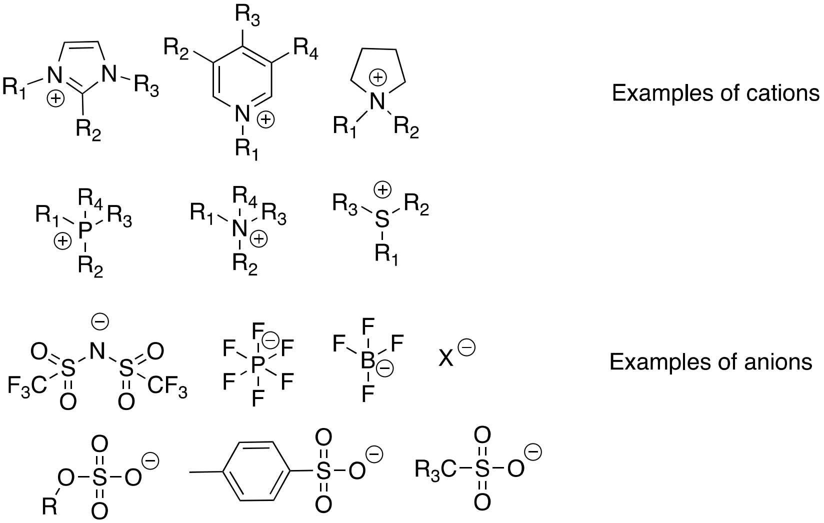


Figure 1.38. *Examples of anions and cations common in ionic liquid chemistry*

The nucleophilic substitution step is generally performed in the presence of solvents, often acetonitrile, at reflux. But it is possible to carry out this type of synthesis without solvent, using ultrasound to fight against the phenomenon of phase separation appearing during the reaction (Estager *et al.* 2007b). The following diagram (Figure 1.39) shows, for example, the *one-pot* synthesis of octylmethylimidazolium triflate ([C_8MIM][OTf]) without solvent and under ultrasonic irradiation.

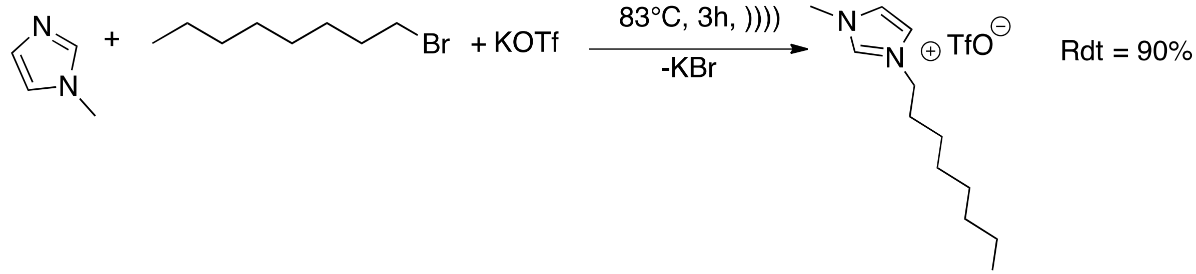


Figure 1.39. *Synthesis of [C_8MIM][OTf] without solvent and under ultrasonic irradiation (adapted from Estager* et al. *2007b)*

During this *one-pot* synthesis, the progressive formation of the bromide anion ionic liquid leads to phase separation because the bromoalkane used as a reagent is not soluble in it. The use of ultrasound thus makes it possible to overcome this effect and obtain good yields for a solvent-free reaction and therefore closer to the principles of green chemistry.

As mentioned above, one of the great advantages of ionic liquids is the great diversity of their properties depending on the anion/cation pair chosen. For example, it is possible to use these *designer-solvents* to solubilize certain poorly soluble compounds, such as cellulose (Swatloski *et al.* 2002). The use of these super-solvents combined with the effects, especially physical effects, of ultrasound can lead to relatively effective extraction systems (Pena-Pereira and Namiesnik 2014).

Among various recent examples, ionic liquid/ultrasonic systems have been used, among others, for the extraction of natural products from biomass, for example the extraction of chlorogenic acid from Ramie leaves (Yang *et al.* 2016) or antimicrobial compounds from *Cinnamomun Cassia* bark (Michalczyk *et al.* 2015). More original examples have also been proposed, such as the micro-extraction of cadmium from biological samples (Khan *et al.* 2015b), fuel desulphurisztion (Dharaskar *et al.* 2014) or the extraction of metals trapped in sediments (Alvarez *et al.* 2017). This coupling effect between a “super-solvent” and ultrasound is very similar to some processes that couple sonochemistry with supercritical fluids.

Various examples of sono-assisted syntheses in ionic liquids are described in the literature such as quinoline synthesis where N-Butyl-N-methylimidazolium tetrafluoroborate is used as a solvent (Heravi 2009) or polyhydroquinoline synthesis by Hantzch reaction catalyzed by a Brønsted acid ionic liquid (Li *et al.* 2015). In many cases, however, there is no mechanically established synergy related to the use of the ionic liquid/ultrasound pair and it is likely that the regularly observed efficiency improvements result from an increase in the temperature of the reaction medium due to the passage of ultrasound through a viscous medium.

For some reactions, however, this “collaborative” aspect between an ionic liquid and ultrasound is clear. In the study of the oxidation reaction of benzyl alcohols to benzaldehydes (Gadilohar *et al.* 2016), a change in the ionic liquid occurs during the passage of the ultrasonic wave, as indicated in the reaction mechanism below (Figure 1.40).

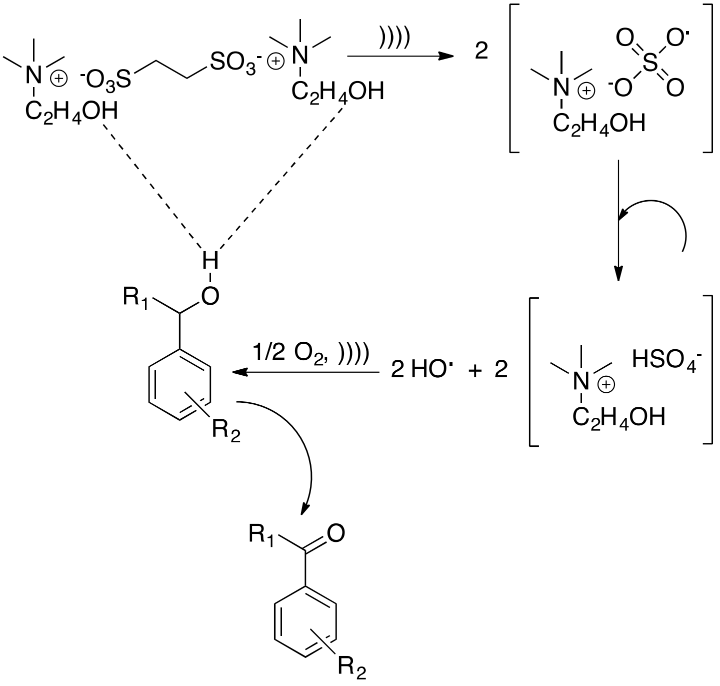


Figure 1.40. *Proposed mechanism for ultrasound-assisted oxidation of benzyl alcohols (adapted from Gadilohar* et al. *2016)*

In this case, the anion of choline peroxodisulfate, a bio-based ionic liquid, is modified by the passage of the ultrasonic wave to form, after reacting with a water molecule, hydroxyl radicals, the active species for this oxidation reaction.

More indirectly, there may be synergy between the physical effects of ultrasound and imidazolium cationic ionic liquids for some reactions, for example Heck reactions (Deshmukh *et al.* 2001) as shown in Figure 1.41.

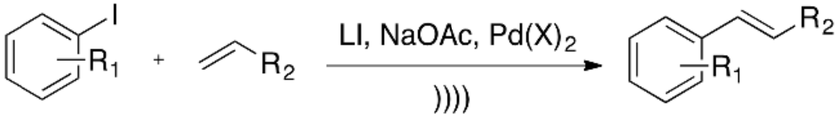


Figure 1.41. *Ultrasound-assisted Heck reaction in ionic liquids based on imidazolium; LI: ionic liquid (adapted from Deshmukh* et al. *2001)*

In this case, the physical effects of ultrasound minimize the particle size of the catalyst, while the ionic liquid with a dialkylimidazolium cation stabilizes it through the formation of carbenes.

This possibility of coupling the “stabilizing” power of ionic liquids to the effects of ultrasound can also be observed for the synthesis of nanoparticles. Vollmer *et al.* have described some examples of sonosynthesis in a review concerning the synthesis of metallic nanoparticles from a carbonyl metal in ionic liquids (Vollmer and Janiak 2011).

1.5.4. *Sonochemistry in water*

Water, a cheap, readily available, non-toxic and non-flammable solvent, is definitely the ultimare solvent in term of green chemistry. Unfortunately, many organic molecules are poorly or not soluble, which compromises its use as a solvent. However, its unique structure and physicochemical properties have the ability to influence the course of an organic chemistry reaction and improve not only its reactivity but also its selectivity (Simon and Li 2012).

Moreover, water is undoubtedly an ideal medium for ultrasound because it promotes cavitation, which is optimal between 318 and 343 K (Severa and Bár 1991). The literature is very rich in publications describing organic chemistry reactions under ultrasound in water. The examples presented in the following only concern experiments for which the use of ultrasound makes it possible to avoid the use of catalysts and/or additives, which would normally be required.

1.5.4.1. *aza-Michael addition reaction*

Michael addition reactions are a very important family of reactions for the creation of carbon-carbon and carbon-heteroatom bonds. They are particularly so with regard to the creation of carbon-nitrogen bonds because they lead to the synthesis of biologically active compounds such as alkaloids, 3-aminoalcohols, β–amino acid esters and other derivatives (Rulev 2011; Amara *et al.* 2013). A large number of solvents and catalysts have been proposed through the description of methods that have unfortunately reached certain limits. These limitations usually concern a significant additional cost or a lower yield. In order to overcome these limitations, it is necessary to use additives or to extend the reaction time, which is not desirable in terms of sustainable development chemistry. Thus, in 2012, Banik and colleagues (Bandyopadhyay *et al.* 2012) proposed an environmentally friendly protocol for the ultrasound-assisted aza-Michael reaction to avoid the use of a catalyst (Figure 1.42).

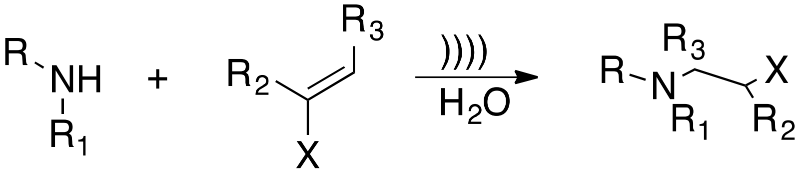


Figure 1.42. *Synthesis without a catalyst and in water of heterocycles via the aza-Michael reaction (adapted from Bandyopadhyay* et al. *2012)*

This new method was tested in a simple ultrasonic bath (f = 42 kHz, $Po_{electric}$ = 135 W), solvent-free, in water and in various organic solvents. High yields have been obtained in water and under solvent-free conditions, but the reaction in water is much faster than in any solvent or even when the reaction is carried out without any solvent. Solvent-free and ultrasonic reactions are three to six times faster than in water under silent conditions. Many amines have been tested on various Michael acceptors under optimized conditions with water as a solvent, resulting in up to 98% Michael adduct in 5 to 10 minutes, with high regio- and chemo-selectivities, without the formation of by-products. Indeed, hydrogen bonds between water and the carbonyl group of the Michael acceptor increase the electrophilic character of its carbon, accentuating the nucleophilic attack by the amine and thus the kinetics of the reaction.

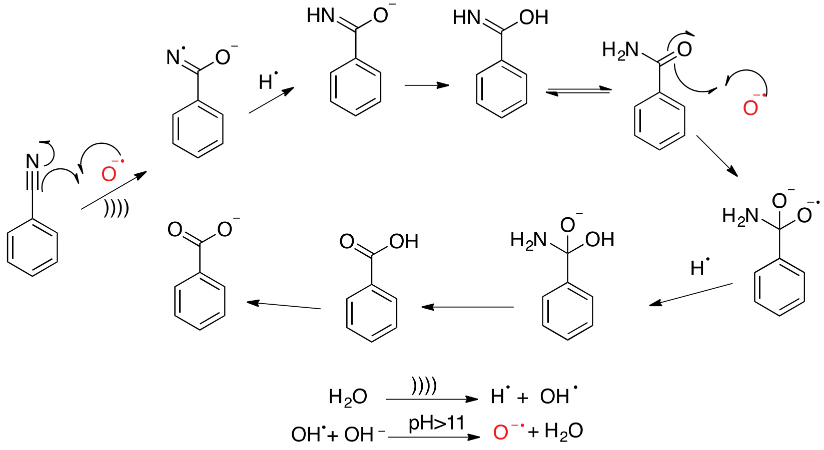
Similarly, the bonds that are formed between the hydrogen on the amine and the oxygen from the water molecule increase the nucleophilic character of the nitrogen of the amine. In addition, the water, at the implosion temperature of the cavitation bubble, behaves like an organic pseudo-solvent. Finally, the mixture is cooled when the reaction is complete and this temperature decrease is accompanied by a decrease in the solubility of the organic compounds, thus facilitating their recovery. In this example, the use of ultrasound as a technique for activating aza-Michael reactions in water allows one to avoid the use of catalysts. The protocols are simple and environmentally friendly, the reactions are fast and the yields in Michael adducts are high.

1.5.4.2. *Hydrolysis reactions*

Nitriles, amides and acids have many applications in the pharmaceutical industry as active pharmaceutical intermediates or drugs, and in the chemical industry for the synthesis of pure enantiomers of chiral compounds (Brady *et al.* 2004). The hydrolysis of nitriles is widely studied because it allows the synthesis of very interesting compounds such as amino acids from aminonitriles, acrylamide from acrylonitrile or adipic acid from adiponitrile (Crosby *et al.* 1994). It is carried out in two distinct stages and requires the use of hard acid or basic conditions at high temperatures due to the low reactivity of the starting nitrile (Pawar and Yadav 2014). Alternatives have been proposed to overcome these problems such as enzymematic biocatalysis (Pawar and Yadav 2014) or organometallic catalysis (Kukushkin and Pombeiro 2005). Nevertheless, ultrasound is an excellent alternative to these catalysts and has proven to be highly effective in the hydrolysis of nitriles to carboxylic acids (Lignier *et al.* 2011). In this work, through the study of the main parameters of the reaction: pH, hydrolysis medium, reaction time and activation technique (heating in an oil bath under silent conditions or use of ultrasound at f = 30 kHz, $P_{acoustics}$ 1.9 W.mL^{-1}), the authors observed that when the reaction is carried out at a pH > 11 under ultrasound, the hydrolysis rate increases significantly and 45 minutes of ultrasonic irradiation is sufficient to selectively obtain 95% benzoic acid. The experiments are performed at a low frequency and yet the high yields and high kinetics are not only explained by the mechanical effects of ultrasound. Based on kinetic studies from the literature, the authors therefore propose a radical mechanism based on the role of the O^{-} radical, which is formed by sonolysis of water at pH > 11 (Figure 1.43). They thus highlight a synergy between the physical and chemical effects of ultrasound.

Under the same operating conditions, adiponitrile is quantitatively converted to adipic acid.

Similarly, an increase of 4 to 15% in the kinetics of acid hydrolysis reactions of many carboxylic acid esters has been observed under ultrasonic activation (Mason 1997). In addition, the effects of ultrasound during the hydrolysis of methyl methanoate at a frequency of 23 kHz have been attributed to an increase in molecular mobility due to pressure gradients associated with the collapse of the cavitation bubble. In addition, an increase of 14 to 15% was observed when 4-nitrophenyl esters were hydrolyzed at 35°C under ultrasonic irradiation (f = 20 kHz) (Figure 1.44).



$$H_2O \xrightarrow{))))} H^{\bullet} + OH^{\bullet}$$

$$OH^{\bullet} + OH^{-} \xrightarrow{pH>11} O^{-\bullet} + H_2O$$

Figure 1.43. *Basic hydrolysis of benzonitrile under ultrasonic activation (adapted from Lignier* et al. *2011). For a color version of this figure, see www.iste.co.uk/malacria/activation.zip*

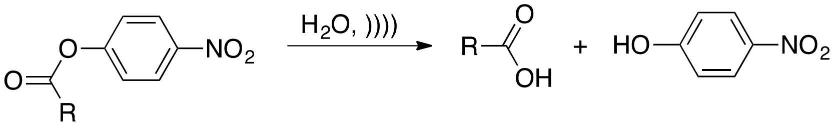


Figure 1.44. *Hydrolysis of esters under ultrasonic irradiation (adapted from Mason 1997)*

The activation energy of hydrolysis activation of each of the substrates varies considerably depending on whether the R substituent of the ester is a Me, an Et, an ^{i}Pr or a ^{t}Bu. Thus, the uniform increase in the rate of hydrolysis cannot be associated with any heating due to cavitation, but rather with the mechanical effects of ultrasound.

1.5.5. *Sonochemistry in glycerol*

The use of solvents from renewable resources has attracted a lot of interest in recent years. For example, glycerol, that is the main co-product of biodiesel production and oleochemistry, is considered a 21st Century commodity. Glycerol is also a solvent of choice for sonochemistry because it allows excellent cavitation (Cintas *et al.* 2014). Thus, in 2011, Cravotto and his collaborators proposed the first ultrasonic syntheses with glycerol as a solvent (Cravotto *et al.* 2011).

1.5.5.1. *Hydrogen transfer reactions*

The authors first implemented the reduction, catalyzed by the dimer Ru(p-cumene)Cl_2, of benzaldehyde to benzyl alcohol in glycerol as solvent and as hydrogen donor. The reaction was performed under microwave irradiation, ultrasound (P = 30 W) and combined microwave/ultrasound irradiation. The crucial role of ultrasound was highlighted during the reduction of benzaldehyde for which the reaction mixture was presonicated (f–10 kHz, P = 100 W) and then heated in an oil bath. At identical yields, these operating conditions allowed a reduction in reaction time by a factor of 2 compared to the reaction without a pre-sonication step. After 3 hours of ultrasonic irradiation, yields of 100% were observed, yields that neither microwave irradiation nor combined microwave/ultrasound irradiation could match (Cravotto *et al.* 2011).

1.5.5.2. *C-C coupling reactions*

Cravotto and his collaborators (Cravotto *et al.* 2011) have also experimented with a series of C-C couplings in glycerol, catalyzed by palladium, by comparing the potentialities of different activation methods. The coupling reaction between 4-iodoanisol and phenylboronic acid in glycerol catalyzed by palladium salts without a ligand, and palladium on charcoal was used as a model reaction. The combination of ultrasonic irradiation/oil bath, microwave irradiation and simultaneous microwave/ultrasonic irradiation considerably increases the reaction rate. The heat supply and the improvement of mass transfer with the combination of ultrasonic irradiation/oil bath and simultaneous microwave/ultrasonic irradiation can explain the excellent yields observed.

The authors then turned to the use of palladium loaded on cross-linked chitosan. In the presence of this catalyst and glycerol as solvent, microwave/high pressure ultrasound and ultrasound/ microwave irradiations significantly increase the reaction efficiency.

1.5.5.3. *The Barbier reaction*

The authors also experimented with the Barbier reaction with benzaldehyde as a substrate (Cravotto *et al.* 2011). They performed the reaction in the conventional THF/NH_4Cl solvent system, under mechanical agitation and in the glycerol/NH_4Cl solvent system under ultrasonic irradiation. The results show that ultrasound increases the yield and kinetics of the reaction by a factor of 1.5. Ultrasonic irradiation using an ultrasonic bath contributes only very slightly to improving the reaction speed, while the ultrasonic probe enables obtaining 80% alcohol in 15 minutes of reaction and 100% in 1 hour, without the formation of by-products.

These results highlight the interest of glycerol as a non-volatile biobased solvent for many organic chemistry reactions. In addition, even if problems of high solubility and viscosity are encountered in this solvent, they can be avoided by increasing the temperature and improving mass transfer through the use of ultrasound.

1.5.6. *Enzymatic chemistry under ultrasound*

Low-frequency ultrasound (20–100 kHz) undeniably improves organic transformations through mechanical effects producing better micro-mixing, microdiffusion and mass transfer, especially in heterogeneous systems (Martin-Aranda and Calvino-Casilda 2010; Chatel and MacFarlane 2014). Based on these effects, ultrasonic activation has been considered to optimize biotechnological processes. Indeed, the cell membrane, under the action of shock waves, is made more permeable, or even fragmented, depending on the acoustic intensity introduced into the system.

This permeability phenomenon seems to be the consequence of oxidation by hydroxyl radicals, resulting from the sonolysis of water, of the fatty chains of phospholipids that constitute the membrane wall of lactobacilli bacteria (Ewe *et al.* 2012). Thus, molecules diffuse better in the reaction medium, up to the complete release of enzymes and proteins, allowing a significant increase in reaction rates (Rokhina *et al.* 2009; Kwiatkowska *et al.* 2011). However, these macromolecules may suffer irreversible damage such as oxidation by the hydroxyl radical (when the reaction is carried out in water), or chain failure due to local shear forces or local hotspot. Thus, it is essential to design the reactor properly using an ultrasonic bath, a cup horn, or an immersion probe (Kwiatkowska *et al.* 2011; Chatel and MacFarlane 2014).

Sonochemistry has already made a significant contribution to the development of biocatalysis, in areas such as sewage sludge treatment and anaerobic digestion (Hogan *et al.* 2004; Pilli *et al.* 2011), decontamination (Entezari *et al.* 2006; Patidar *et al.* 2012; Malani *et al.* 2014), microbial fermentations (Singh *et al.* 2015), enzyme pre-treatment (Shah and Gupta 2008; Zheng *et al.* 2012; Adulkar and Rathod 2014), or biodiesel production (Naveena *et al.* 2015; Subhedar and Gogate 2016). In the latter case, ultrasonic activation makes it possible to reduce the quantity of methanol introduced (Subhedar *et al.* 2015), and of course to recover waste from agro-resources (Adewale *et al.* 2015).

We will focus on recent synthetic transformations activated by ultrasound, mainly transesterification and esterification, leading to high value-added compounds of interest to the pharmaceutical, food and cosmetic industries. In most of the cases presented, biosourced products are used.

1.5.6.1. *Transesterification reactions*

The most representative transesterification reactions are catalyzed by lipases. In aqueous media, these enzymes hydrolyze fatty esters, such as triacylglycerol. But, surprisingly, transesterification reactions are required in organic solvents. Thus, the thermophilic enzyme lipase B, extracted from *Candida antarctica*, is fixed on an acrylic resin, and is called Novozym®435. It behaves perfectly under ultrasound up to 70°C.

The first work involving glycerol was carried out in propan-2-ol in the presence of methyl benzoate in a 37 kHz ultrasonic bath. 1-glyceryl benzoate is then obtained in modest yields (Ceni *et al.* 2011). This transformation has led to the glycerolysis of natural fatty esters such as those extracted from olive oil (Fiametti *et al.* 2012). The resulting mono- and diglycerides are used in the fight against obesity.

Biocatalysis derives its benefits from the excellent regio- and stereoselectivities observed during transformations. It is perfectly applicable to sugar chemistry because it does not require protection and deprotection steps, reduces separation phases and thus leads to a higher overall yield. Thus, Novozym®435 catalyzes the transesterification or direct esterification of a model molecule, glucose, in a supersaturated solution in ionic liquids. The glycosyl fatty monoesters then precipitate into the medium, preventing a double reaction and making processing easier. 1-Butyl-3-methylimidazolium triflate provides the best conversions to surfactant compounds from vinyl laurate (90%) or lauric acid (80%) (Lee *et al.* 2008).

The acylation of natural compounds of the sugar or glycoside family makes these molecules more lipophilic. It is thus possible to directly acylate the natural polysaccharide Konjac glucomannan in a 20 kHz ultrasonic bath in an alcoholic medium in the C6-OH position

(Chen *et al.* 2008). Among the 13 enzymes studied, Novozym®435 catalyzes transesterification in the presence of vinyl esters with the highest yields. The functionalized sugar obtained, with surfactant properties, has a high degree of substitution compared to that observed when the reaction is carried out by enzymatic catalysis alone, which is also slower.

The same reaction was applied to mangiferin, a xanthonoid extracted from mangoes and has a high pharmacological potential. The expected esters are expected to develop increased biological activities due to their greater ability to cross the blood-brain barrier. They are formed exclusively in the C6'-OH position of the glucose part, under mild conditions at 45°C in DMSO in the presence of the PLC enzyme. Under ultrasound, the conversion to acetate is greatest with 84% (Figure 1.45) (Wang *et al.* 2010).

For the same reasons, troxerutin (flavonoid also known as vitamin P4) is acylated with divinyl fatty chain diesters in the presence of alkaline protease (extracted from *Bacillus subtilis*) at 50°C in pyridine. Ultrasonic activation has been studied at different frequencies and powers. Yields double depending on whether the medium is magnetically stirred or under 80 kHz (Figure 1.45) (Xiao *et al.* 2011).

4'-acetoxyresveratrol has increased metabolic stability compared to resveratrol. The latter, a natural derivative of stilbene derived from fruits, particularly grapes, is used for its antioxidant, anti-tumor, anti-inflammatory properties, as well as for its ability to protect the heart muscle. Novozym®435 is a very effective catalyst for its transesterification, under ultrasound at 60°C, with excellent regioselectivity in favor of the phenolic group at the 4' position. The conversion is almost complete and the reaction time is divided by at least 2.4, in accordance with the established kinetic model (Figure 1.45) (Kuo *et al.* 2013).

This biocatalytic system activated under ultrasound at 25 kHz is applicable to the synthesis of fragrances or flavors such as cinnamyl acetate, without a solvent and in 20 minutes. Under these conditions, Novozym®435 can be recycled seven times without any significant loss of activity (Tomke and Rathod 2015).

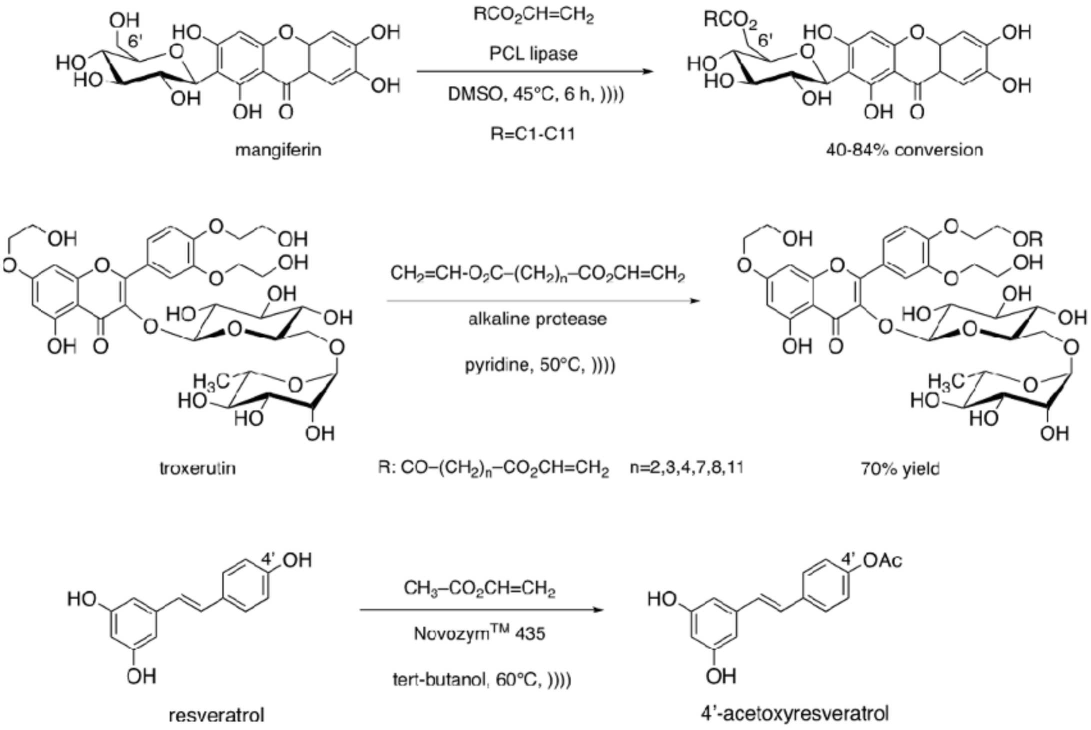


Figure 1.45. *Ultrasound-assisted transesterification of mangiferin, troxerutin and resveratrol (adapted from Wang* et al. *2010; Xiao et al. 2011; Kuo* et al. *2013)*

Such a process has proved to be useful for the production of biodegradable polymers or biopolymers. Thus, polyethylene glutarate is synthesized from ethylene glycol and diethyl glutarate for the first time in the presence of lipase B immobilized on methacrylate polymer (CALBTM Fermase 10,000), without solvent, in 7 hours at 45 kHz vs. 24 hours under silent conditions. Ultrasound can increase the conversion and degree of polymerization (Zhao *et al.* 2016).

Polyhydroxyalkanoates (PHAs) are widely used biopolymers because of their recyclability. They can be derived from opening and then transesterification followed by polymerization of ε-caprolactone in an ionic liquid medium [emim][BF_4] (Gumel *et al.* 2012). Among the four enzymes studied, Novozym®435 gave the best results due to its greater stability under ultrasound. Indeed, the conversion is 70% in 20 minutes at 35 kHz, the polymer having a higher average molecular weight, a higher degree of crystallinity, and a lower polydispersity. The viscosity of the ionic liquid limiting mass transfer is countered by ultrasound, allowing a more efficient micro-mixing. This biocatalytic process was used during the ring opening and copolymerization of γ-butyrolactone and ε-caprolactone, this time in chloroform, to poly-4-hydroxybutyrate-*co*-6-hydroxyhexanoate (Gumel *et al.* 2013). The contribution of ultrasound is once again undeniable, leading to the copolymer with optimized characteristics.

However, transesterification is not effective in terms of atom economy. Also, direct biocatalyzed esterification has also been considered under ultrasonic activation.

1.5.6.2. *Esterification reactions*

Esterification reactions are also catalyzed by lipases in non-aqueous media. Most often, the carboxylic acid reacts with an excess of alcohol with or without solvents.

In the latter case, isoamyl butyrate, a fruity aroma, is synthesized almost quantitatively in 3 hours at 60°C at 25 kHz, instead of 10 hours under silent conditions (Bansode and Rathod 2014). Novozym®435 can then be recycled seven times without any significant loss of activity.

This work continued with the synthesis of waxy fatty esters, used in cosmetology, biocatalyzed by Fermase CALBTM 10,000 (Khan *et al.* 2015a). The cetyl oleate yield is multiplied by 7.5 under ultrasound at 40 kHz if compared to conventional conditions, and in accordance with the kinetic model.

Other fatty acid esters, derived from plants, have been produced by direct esterification, with modest yields for ascorbyl palmitate (Lerin *et al.* 2011), and excellent yields for the corresponding oleate, although a very large excess of oleic acid is required (Balen *et al.* 2015). A solvent is essential to ensure the dissolution of the starting materials.

Other esters, derived from primary and secondary alcohols with short carbon chains and acids ranging from C4 to C18, have been synthesized for application in perfumery or in the food industry. The biosynthetic strategy makes it possible to attribute to them the quality of “natural flavors”. The enzyme used here is phospholipase Lecitase-Ultra, immobilized on divinylbenzene styrene beads (MCI-Lecitase) (Alves *et al.* 2015). Ultrasound leads to a higher initial reaction rate in a medium more concentrated in starting substrates. The best yields are thus obtained for esters resulting from C8 to C14 acids.

The pharmaceutical field is not to be outdone since methyl caffeate, with interesting antitumor properties, is synthesized almost quantitatively by direct esterification in a bis(trifluoromethane) sulfonimide hydrophobic ionic methanol-liquid mixture of 1-butyl-3-methylimidazolium (Wang *et al.* 2015). Novozym®435 is once again effective and is recycled 16 times, with a decrease in yield after 11 cycles.

Finally, racemic ibuprofen is resolved by enantioselective esterification (Baiyi *et al.* 2016). The (R) acid reacts with octanol in the presence of an immobilized thermophilic esterase APE1547 at 45°C in *n*-heptane, leaving the desired enantiomer (S) unchanged. Ultrasonic activation saves time (2.5 hours of reaction) and enantioselectivity, without changing the properties of the enzyme during the 10 reuse cycles.

Chemists who work with enzymes are increasingly interested in molecules of therapeutic interest. Other reactions are thus developed using the combination of biocatalysis and ultrasound.

1.5.6.3. *Other reactions*

While enantioselective reduction reactions have increased with the development of homogeneous catalysis, examples of sonochemical bioreduction are rare.

However, the biotransformation of 1-(3-hydroxyphenyl)-2-(methyl-amino)-ethanone (HPMAE) into (R)-phenylephrine (a potent vasoconstrictor and ephedrine substitute) is an example of choice (Zang *et al.* 2015). The biocatalyst is introduced into the reaction medium as *S. marcescens* N10612 cells (Figure 1.46). Conversion reaches more than 95% in just 10 minutes in an ultrasonic bath compared to 24 hours under conventional stirring conditions. This result comes from the increased permeability of cells under ultrasonic activation.

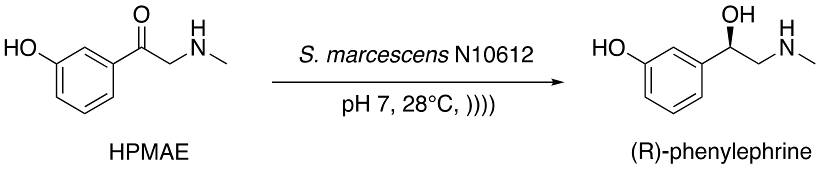


Figure 1.46. *Enantiospecific biocatalytic reduction of HPMAE to (R)-phenylephrine (adapted from Zang* et al. *2015)*

The last figure in this section concerns the one-pot synthesis of indolizines catalyzed by *Candida antarctica* A and B lipases, under ultrasound tank activation (Figure 1.47) (Dinica *et al.* 2013). This cyclo-addition proceeded thanks to the *in situ* formation of a yide, which can react in this aqueous medium. The reaction is tremendously accelerated under ultrasound, leading to more than 70% conversion in the presence of the enzyme *Candida antarctica* A in 2 hours as opposed to 2 days under silent conditions. Here, several principles of green chemistry are respected, making this unique synthesis very effective.

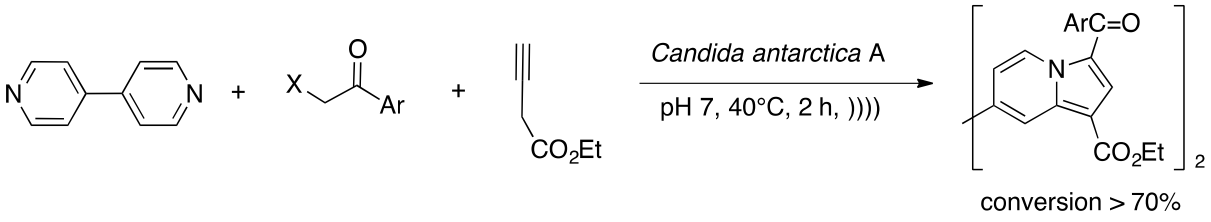


Figure 1.47. *Biocatalyzed one-pot synthesis of indolizines by cyclo-addition (adapted from Dinica* et al. *2013)*

1.5.7. *Sonoelectrosynthesis*

By allowing chemical phenomena to be generated not by adding different products but by simply passing electrons through a medium, electrochemistry is undeniably one of the techniques of interest for green chemistry. The coupling of electrochemistry and ultrasound is an old technique and since the 1930s, among others, Schmid and Ehret were already studying the effect of ultrasound in metal passivation (Schmid and Ehret 1937). Ultrasound can be extremely beneficial in sonoelectrochemistry, whether through physical effects such as mass transfer (including electrochemically generated active species) and electrode surface cleaning or chemical effects (radical formation).

This synergy has been used in various traditional fields of electrochemistry, for example in electroplating (Walker 1993) where ultrasound allows an increase in the thickness of the deposited layer, an improvement in cathodic efficiency, or an improvement in the hardness of the deposited metal layer. Various fields such as corrosion, organic chemistry, polymerization or the production of nanomaterials have benefited from this technique (Pollet and Hihn 2012).

1.6. Conclusion

Despite its many assets, the use of ultrasound in organic chemistry has a number of limitations, mainly related to the principles and uses of sonochemistry:

– *the reproducibility* of experiments related to the geometry of the reactor used, the type of ultrasonic probe, the nature and concentration of dissolved gases;

– *the homogeneity of the ultrasonic field* related to the geometric parameters of the ultrasonic reactor that modify the acoustic cavitation conditions;

– *the determination of the ultrasonic power*, which is not always possible in an organic medium, and which can be modified during a possible transformation of the reagents contained in the system and the progressive formation of the reaction products;

– *the scale-up* that the many parameters and physical phenomena involved in organic sonochemistry associated with certain technological limitations make difficult.

Nevertheless, since it has become possible to produce it, ultrasound has found a large number of varied applications, whether for submarine detection, to fight against dirt, fouling and rust on ship hulls, to detect defects inside a material, for medical applications or for the synthesis of organic molecules. In this field, sonochemistry can provide simple solutions to some problems in organic synthesis, but it is still a very complex field to analyze from a theoretical point of view.

However, although the phenomenon of cavitation is not fully understood, it is now possible to rationalize the effect of ultrasound in organic chemistry. Indeed, while the kinetics of some reactions increase without modification of the products, others are accompanied by inversion phenomena that highlight the contribution of acoustic cavitation or even the intervention of electron transfer processes.

Sonochemistry is now much more reproducible than it was a few years ago when only ultrasonic baths were available. Indeed, the appearance of ultrasonic probes and standardized systems has enabled enormous progress in terms of the reproducibility of experiments.

In addition, the efficiency of sonochemistry can also be made available to other techniques such as electrochemistry or improved by combining it with other techniques such as microwave irradiation.

Nevertheless, scaling up remains the main challenge in the use of ultrasound in organic chemistry. However, organic sonochemistry conducted on an industrial scale would undoubtedly have a large economic impact, not only because of its potential but also because it is in line with the objectives of "green" chemistry or "chemistry for sustainable development". This could undoubtedly be a decisive factor in the use of ultrasound in organic synthesis.

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