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Sonochemistry in non-conventional, green solvents or solvent-free reactions

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ABSTRACT

Few decades ago, the expertise gained from well-established extraction, processing and degradation techniques, paved the way for the use of ultrasounds as an alternative energy source in chemistry. Among other peculiar features, the locally extreme temperatures and pressures resulting from cavitation, proved to efficiently trigger reactions while maintaining mild average conditions, enhancing rates and yields and, hence, contributing to increase the popularity of sonochemistry up to the present level. The physical properties of the irradiated mixture are crucial for the effectiveness of cavitation, as well as for the proper transfer of acoustic energy to reactants. Therefore, the choice of a solvent that meets these requirements, while minimizing the environmental impact of the process is a fundamental one. Studies that combine sonochemistry with green, non-conventional solvents or with no solvents are surveyed in this review, evidencing how the most frequently investigated options are water phase, ionic liquids, followed by ethylene glycol and its oligomers, glycerol and few other biomass-based solvents. Numerous solvent-free, ultrasound-promoted procedures are also reported in the literature and are included in this contribution. The vast majority of the examples gathered here describe organic reactions, syntheses of nanosystems and polymerizations.

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1. Introduction

Acoustic waves that fall in the human hearing range (*i.e.* 'sonic' waves) have frequencies that cover the 20 Hz - 20 KHz interval. Below and above these extremes the 'infrasounds' and 'ultrasounds' (US) lie, respectively. They constitute the basis for a number of applications in science and technology and are further subdivided into 'power US' (20 KHz to 1 MHz) and 'high frequency US' (1 MHz upwards) according to their use as energy source or as tools for therapeutic and diagnostic application, at low intensity waves. A rapidly increasing number of scientific publications demonstrate how power US can replace conventional heating/stirring methods as the energy source for chemical reactions, with particular emphasis on organic and polymerization reactions and synthesis of inorganic nanostructures. Several reviews can be found in the literature covering different fields of sonochemistry, such as organic transformations and catalysis,[1–8] polymer science,[9–11] surface modification,[12] and design and scale-up of US reactors.[13,14,15] Nonetheless, to the best of our knowledge, an up-to-date review on the use of environmentally benign solvents in sonochemical synthesis has not been published, while it is important to underscore the advantages deriving from the efficient coupling of these two sustainable approaches. Hence, the following paragraphs contain a comprehensive survey of papers that combine sonochemical reactors with 'green' solvent systems or non-conventional media for organic synthesis such as ionic liquids (ILs). These are subdivided according to the employed solvent and, further, according to the class of the described chemical reaction. Results are discussed critically, stressing the benefits or drawbacks brought by the use of ultrasounds as the energy source, covering the scientific literature up to the first trimester 2016. Examples of reactions performed in mixture of binary systems involving volatile organic solvents and green solvents are out of the scope of the review and are not described.

1.1. Acoustics in liquid media

Sound waves consist in alternating compression and decompression of a gaseous, liquid or solid medium possessing elastic properties. Waves propagate longitudinally (through any kind of medium) or transversely (through solids only). Dealing here with US-enhanced chemical reactivity (*i.e.* sonochemistry), liquids are the only acoustic media of practical concern, and transverse waves will not be considered. Under the effect of a sonic wave the acoustic pressure P_a at a given distance from the source oscillates according to the equation[16]

$$P_a = P_A \sin 2\pi f t$$

where P_A is the maximum acoustic pressure of the wave and f is the frequency. It is useful to define the intensity of a wave, I, as the energy flowing per unit area and time (usually expressed in W cm^{-2}). Intensity I is related to the maximum acoustic pressure, P_A, by the equation

$$I = P_a^2 \big/ 2\rho c$$

where ρ is the density of the medium and c is the speed of the sound in the medium. As the distance from the acoustic source, l, increases, the intensity of the wave tends to decrease from the initial value, I_0, because of absorption phenomena such as viscous or frictional interactions between molecules of the medium. Hence, the absorption coefficient, α, is an important parameter to introduce:

$$I = I_0 e^{-2\alpha l}$$

α depending on the density (ρ) and viscosity (η) of the medium:

$$\alpha = \frac{8\eta_s \pi^2 f^2}{3\rho c^3}$$

α can be modified to take into account temperature losses in the medium according to the equation

$$\alpha = \frac{2\pi^2 f^2}{\rho c^3}\left[\frac{4\eta_s}{3} + \frac{(\gamma - 1)K}{C_p}\right]$$

where γ is the ratio of heat capacity at constant pressure, C_p, at constant volume and K is the thermal conductivity of the medium. The absorption coefficient has a great practical significance since it indicates how efficiently acoustic energy is transferred to the reaction mixture, one of the parameters to take into account when selecting the suitable solvent to perform the synthesis.

Solvent choice is crucial in sonochemistry because the combined use of solvent and US can dramatically influence the reactivity and the product yield, however, only few studies report the solvent properties/sonochemistry relationship.[17,18] The efficiency of a sonochemical reaction is expressed by the dissipated ultrasonic power (U_p) into the bulk medium, related to the extent of cavitation, whose the intensity is directly related to: the greater the power, the greater is the cavitation effect. Cohesive forces in the solvent oppose to negative pressure required for cavitation, retarding the formation of cavitation bubbles. Therefore, in viscous solvents the onset of cavitation is longer but the dissipated power is higher. Indeed, when using less volatile organic liquids, the bubble content depends by the reactants rather than the solvent vapour. The formation of liquid/gas interfaces is fundamental for cavitation and solvents with low surface tension should show higher

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Table 1
Average ultrasonic dissipated pressure (U_p) and physical properties of several solvents.

Solvent	Vapour pressure (kPa)	Viscosity (mPa.s)[a]	Surface tension (Dyn/cm)[b]	U_p (W)[c]
Acetone	24.53	0.33	23.3	1.98
Chloroform	26.66	0.57	27.1	1.93
Methanol	12.8	0.6	22.6	2.93
Hexane	16	0.31	18.4	2.46
Ethanol	5.9	1.08	22.3	3.47
Benzene	42.66	0.65	28.9	2.91
CH_3CN	9.7	0.38	29.1	3.40
1-Propanol	2.77	1.72	23.7	4.00
Water	2.4	0.89	72.75	6.35
Toluene	2.90	0.59	28.5	2.87
1-Butanol	16.66	3.0	24.6	4.61
Acetic Acid	1.5	1.13	27.4	4.72
DMSO	0.06	2	43.7	5.5
[BMIM][BF_4]	0	219	46.6	7.02

[a] Determined at 25 °C.
[b] Determined at 20 °C.
[c] Average ultrasonic dissipated pressure (U_p) at 20, 25 and 30% amplitude (A) determined by calorimetric method.

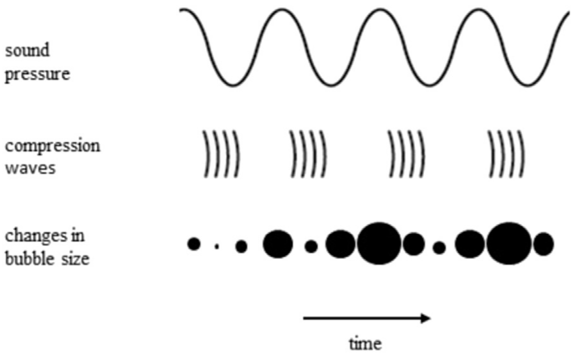

Fig. 2. Schematic representation of the cavitation phenomenon.

dissipated powers and although the correlation between vapour pressure and cavitation energy is not always linear, a recent study reported the relationship between the heating profile of several solvents and the dissipated powers (Table 1).[17] Solvent such as water, ionic liquid as [BMIM][BF_4] or glycerol[19] are an excellent choice in sonochemistry: their high surface tension correlate to a high dissipation power, leading to an important energy release upon bubbles implosion. On the contrarily, the dissipated ultrasonic power (U_p) decreases for solvents with high volatility such as CH_2Cl_2, $CHCl_3$ or acetone (Table 1) or as a function of the amplitude (A) of the irradiation (Fig. 1). Hence, a decrease of the vapour pressure of the solvent enhances cavitation intensity and consequently the rates of sonochemical reaction.[20]

If the vapour pressure of the liquid is increased by raising the temperature of the sonochemical reaction, cavitation will be improved, however less violent collapse of bubbles has to be expected, according to the so-called anti-Arrhenius effect.[21] Therefore, higher reaction rates can be achieved if the temperature is decreased to a lower limit imposed by the viscosity of the solvent, or in a solvent with low vapour pressure. Taking into account that temperature changes affect the viscosity of the solvent, a linear correlation exists with between these variable of the system and the dissipated power, although this correlation can not be generalized for all the solvents. Last, but not least, also dissolved gases may have a major influence on the sonochemical efficiency, directly linked to the production of cavitation bubbles.

1.2. *Cavitation and sonochemistry*

During the decompression phase of a power US wave, the molecules of a liquid may experience forces strong enough to outbalance Van Der Waals interactions and, locally separate them from each other. When this happens, some very small cavities are formed in the bulk, cavities that tend to expand until the pressure is low enough to sustain their growth. At this stage any component of the reaction mixture may evaporate into the void and reduce the negative pressure bias between the inside of the cavity and the surrounding liquid. After a few compression-decompression cycles, the cavity can either be sustained by vapours and become a bubble with a life time long enough to reach macroscopic dimensions, or instead implode violently producing hot-spots with rather extreme temperatures and pressures of around 5000 K and 1000 atm (Fig. 2).[22,23] Because of this very peculiar phenomenon, sonication is capable of quickly providing the activation energies needed to trigger chemical reactions, while maintaining the average conditions of the mixture relatively mild.

In comparison to traditional activation methods (thermal, microwave, photochemistry, etc.),[24] sonochemistry occupies a unique place, providing unusual reaction conditions and prohibitive

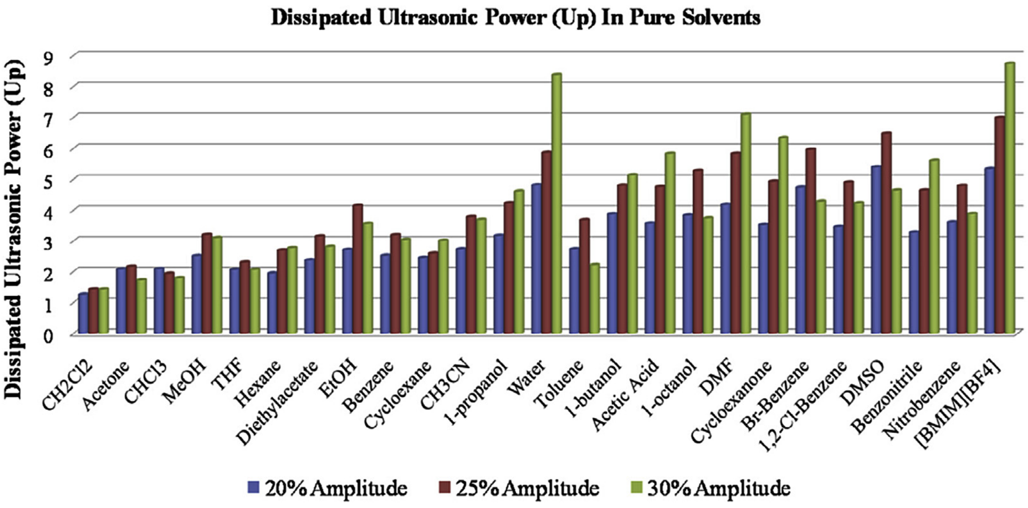

Fig. 1. Dissipated ultrasonic power (U_p) for each solvent at different amplitudes methods (Image reproduced from Ref. [17] with permission from Elsevier).

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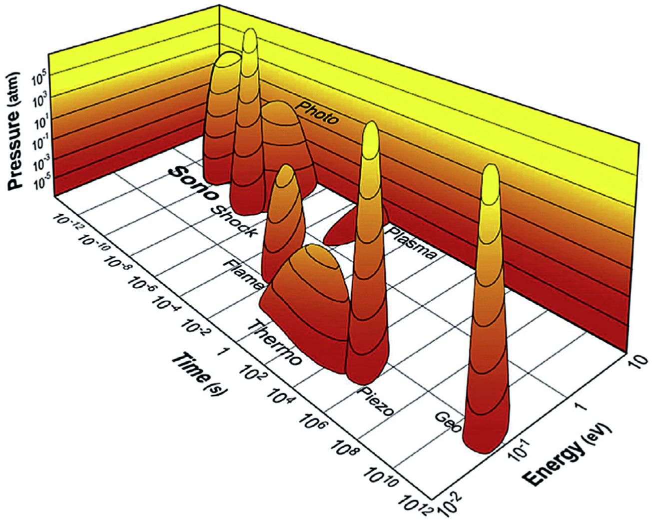


Fig. 3. Energy impact proved by ultrasound in comparison with other activation methods (Image reproduced from Ref. [26] with permission from The Royal Society of Chemistry).

thermal activation barriers similarly to mechanochemistry.[25,26] At molecular level, there is no direct interaction between ultrasound and chemical species, being the molecular dimension too small compared to the acoustic wavelength. The kinetic energy that drives the chemical reaction is provided by the acoustic cavitation, responsible for the high-pressure, high-temperature and high-energy profiles[26,27] locally supplied to the molecules for a very short time (Fig. 3). Indeed, it has been estimated that the cavitation event stands for less than 100 ns and that the "hot spots" cool down at a rate of 10^{10} K s^{-1}.[28]

The extent of cavitation strongly depends on the intensity and frequency of ultrasonic waves. A higher intensity facilitates the formation of cavities since molecules in the bulk are subjected to higher pulling and pushing forces. Hence, not only the generation of void is more likely, but also the implosion tends to be more violent. There is normally an upper limit to amplitude of waves that is imposed by the resistance of the sonication apparatus. Higher frequencies, on the other hand, harness the process by reducing the lapse of time available for molecules to overcome interactions and separate, before the wave period comes to completion. Every other parameter being kept constant, a liquid with higher frequency US requires more power from the probe to cavitate. Although of minor relevance in some conventional reaction set ups, it is worth noting here that the physical properties of the reaction mixture are extremely important in sonochemistry. Considering the physics of wave propagation and attenuation (Paragraph 1.1) as well as the basis of cavitation, it is evident that density, viscosity, vapour pressure, surface tension and heat capacities may all influence the efficacy of an US-promoted process. The presence of microscopic solid impurities in the liquid is also a crucial factor favouring cavitation, since even very small air pockets embedded in the particles surface have a marked nucleating effect for bubbles.

Sonochemistry is often subdivided in two categories of reactions in which the US enhancement results from different reasons. Nonetheless, these beneficial effects can coexist and cooperate in the same chemical transformation.

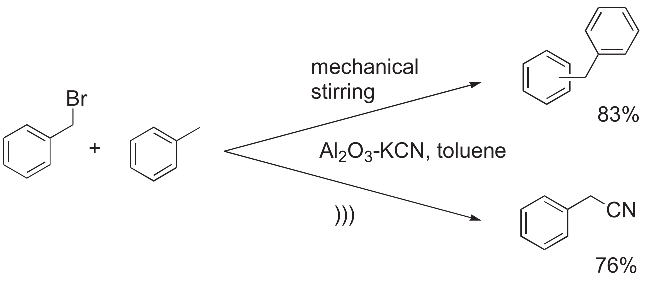
- Homogeneous reactions with radical intermediates may be accelerated by cavitation when sufficiently volatile reactants enter the cavity where the formation of the radical species is favoured. Solvent molecules can also undergo bond cleavage and act as indirect source of radicals for less volatile substrates, which in any case experience strong shock waves from nearby imploding cavities.
- Heterogeneous reactions or catalysis promoted by nanoparticles can benefit from the vigorous and diffuse agitation provided by sound waves, maximizing contact between phases. Even more important, the implosion of cavities in the proximity of a solid surface produces very intense streams of liquid (*i.e.* micro-jets) that impact and 'clean' or even disintegrate the outer layers of the solid. In the case of a metal nanoparticle-based catalyst, the micro-jet effect constantly increases and renews the exposed area of 'clean' particle surfaces and, hence, boosts and prolongs the catalyst activity. Solid reactants (*e.g.* in a suspension) are similarly activated by US-induced micro-jets since their contact with the rest of the mixture are markedly improved by the rapid and efficient fragmentation of aggregates and by the collapse with the other reaction components, in a fashion resembling the principles of mechanochemistry brought to extreme conditions.[26,29,30]

Sonochemical acceleration of homogeneous ionic reactions is rarely described and generally less remarkable from a quantitative point of view. However, accurate kinetic analyses suggest that variation in reagents or intermediates solvation may lead to a reduction in activation energy and hence in a rate enhancement.[31]

Interestingly, using US as the energy source can accelerate a chemical reaction but also alter its selectivity. This phenomenon was firstly observed by Ando and co-workers[32] during sonication of benzyl bromide in an alumina-supported potassium cyanide toluene suspension. Benzyl cyanide was obtained in good yield as the result of an aliphatic nucleophilic substitution, while under conventional oil-bath heating the reaction product consisted in a mixture of regioisomer phenyl-tolyl methanes coming from a Friedel-Crafts reaction (Scheme 1).

An even more outstanding selectivity switch was reported by Moore and co-workers[33] who studied the US-promoted electrocyclic ring cleavage of a benzocyclobutene bearing a poly(ethylene glycol) (PEG) chain at each cyclobutene side. Both *cis*- and *trans*-cyclobutene derivatives yielded the same (*E,E*) isomeric diene, violating the Woodward-Hoffmann rules on the conservation of orbital symmetry (Scheme 2). Provided a molecular weight higher than a threshold value of typically 30–40 kDa, polymers can thus be employed as 'mechanophores' to channel acoustic energy[34] towards target bonds and force a reaction toward a normally disfavoured pathway or direction, as also observed for retro Diels-Alder,[35] metal-ligand de-coordination,[36,37] or 1,2,3-triazole 'unclicking',[38] or metal-catalysed cyanation[39] reactions.

The activation of hard metal surfaces is another outstanding feature related to the use of US irradiation and successfully applied to the preparation of 1,4-disubstituted 1,2,3-triazole derivatives from azides (including cyclodextrine derivatives) and alkynes using



Scheme 1. Reaction modified by ultrasound activation.

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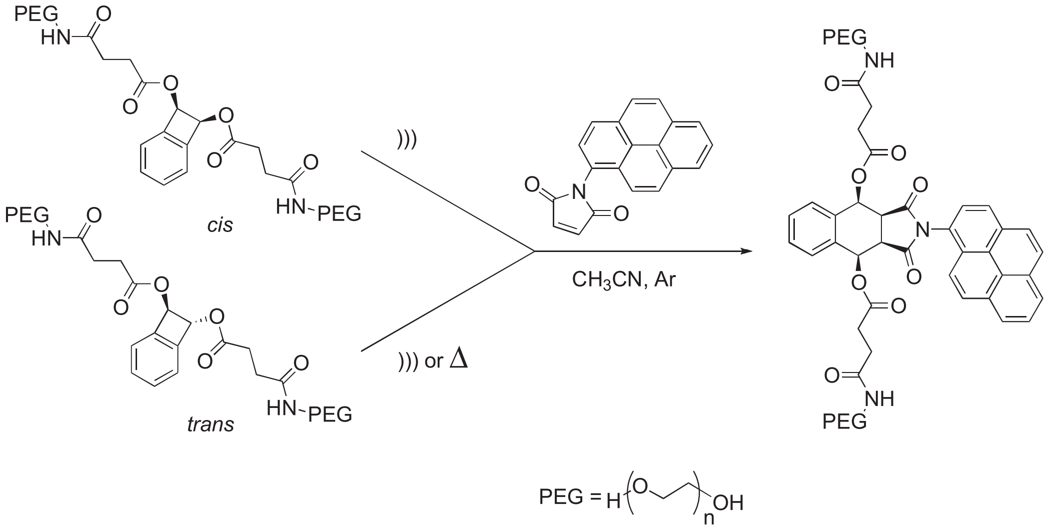
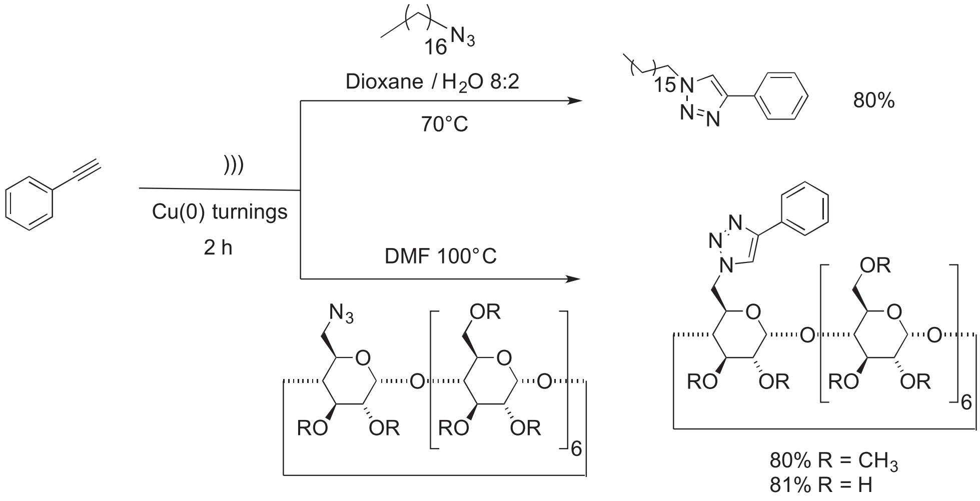


Scheme 2. Effect of polymer on the selectivity during sonochemical activation.



Scheme 3. US-assisted metal surface activation in Cu-catalysed azide-alkyne cycloaddition reaction (CuAAC).

metallic copper[40] (Scheme 3).

The Cu-catalysed azide-alkyne cycloaddition reaction (CuAAC) takes place because the passivated layers were efficiently cleaned and activated by ultrasonic waves through jets created by micro-turbulences during cavitation. This allowed an interaction of the reaction partners by promoting both their diffusion from the solution to the metal center and the electron transfer from the metal to the organic substrates.

The importance of ultrasound was also demonstrated for the intensification of biodiesel production processes. Yields and the reaction rate of the transesterification reaction were improved. Hence, emulsification induced by ultrasonic irradiation increased the mass transfer between immiscible reagents or multi-phase reaction mixtures,[41] in solvent-free conditions[42] or using heterogeneous catalysts.[43] In the last case, cavitation generated new active surface areas, disintegrating the solid catalysts into smaller particles while maximizing the interfacial surface.

1.3. *Devices for ultrasound's generation*

The phenomenon of cavitation is not a recent discovery as it has already been detected and described in the late nineteenth as the origin of erosion damages on boat propellers' metal surfaces. Nonetheless in the 1980s, modern US equipment became widespread, relatively inexpensive laboratory tools, and allowed to perform sonochemistry in an effective and controlled fashion. Nowadays, generation of ultrasonic waves is achieved by the use of piezoelectric materials subjected to an electrical potential alternating with a frequency at a determined value in the US range. However, the transmission of mechanical oscillations to the reaction mixture can be engineered in two quite different layouts.

- Sonication probes (*i.e.* direct sonicators) are titanium alloy rods connected to the US generator and directly immersed into the reaction mixture, avoiding the direct contact between the probe and the reaction vessel, while keeping at the minimum the space between them (dead zone). A careful choice or design of the vessel is essential to optimize the interaction between the sample and the zones of maximum cavitation, taking into account that the intensity of ultrasound decreases quickly from the probe, both axially and radially. The probe tip can have different geometries: small diameters (microtips probes) deliver

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focused, high-intensity sonication, while large diameters allow better treatment of large volumes at the expense of intensity. Although virtually not utilized for chemical synthesis, probes made of other materials than Ti-alloys, including silica glass or Teflon, may be used in case of particular requisites to avoid contamination with metals (*e.g.* in case of bioassays or trace analysis) or for corrosive samples, Al-alloys for polymer welding and hardened steel for high wear/low amplitude applications. Nonetheless, it is worth noting that the transmitted US intensity varies with the probe material[44] and that fragile probes (like silica glass probes) impose limitations on the power output settings. Ceramics, quartz,[45] or engineered plastics[46] such as PEEK (polyether ether ketone) or PTFE (polytetrafluoroethylene) can also be used, usually exhibiting high chemical and temperature shock resistance. The majority of high intensity horn operate at 20 or 40 kHz, with cavitation occurring from tens of Hz to tens of MHz. However, the intrinsic viscosity of liquids prevents cavitation above that frequency regime.

- Sonication (cleaning) baths (*i.e.* indirect sonicators) transmit acoustic waves from one or multiple metal horns to a volume of water in which the reaction tube is immersed, avoiding contact between the mixture and any part of the equipment. Although normally a lower US intensity is attainable, baths are useful when contamination or sample loss must be prevented, as well as for the treatment of several samples at the same time. Common US cleaning baths operate at very low acoustic intensities but possess the same construction scheme. Most of the cleaning baths operate near 40 kHz, but few hundred kHz to few MHz regime are also available.

The choice of the ultrasonic device relies both on the type of application and the reproducibility and reliability of the method.

Emulsification and surface damage are dominant at lower frequencies, while full frequency rage is necessary to produce cavitation. Therefore, ultrasonic (cleaning) baths are mainly used for liquid-solid reactions involving reactive solids such as Li or Mg, which are easily passivated. Unfortunately, the intensity delivered by cleaning baths is insufficient for most applications and they suffer of lack of reproducibility, due to their odd geometry, with the frequency and the power depending on the transducer used. Highly recommended are the ultrasonic probe equipment, delivering higher amount of ultrasonic power, which is directly related to the magnitude of vibration of the tip. The possibility to control the power input to the transducer, to programme parameters such as amplitude, pulse, and to monitor the rise in temperature over the time ensures high reproducibility. Nonetheless, the reproducibility of a sonochemical reaction is also frequency and apparatus dependent. Indeed, the number of cavitating bubbles is determined by both the presence of standing waves (especially at higher frequencies) and the volume of the reactor where bubbles are formed.

Taking into account that the physical characteristics of the medium determine the ultrasonic energy entering the chemical system an accurate control of the temperature is fundamental to maintain the optimum cavitation. Diverse solution can be adopted: i) the use of pulsed radiation to dissipate the energy; ii) by designing vessels incorporating a cooling system such as a water jacket or iii) cooling down the reaction mixture with an ice bath, while monitoring the temperature continuously.

Another very interesting approach towards more reliable and cost-effective synthetic transformations consists in the combination of different sources of energy with their own specific effects. Since microwaves (MW) and US allow different irradiation mechanisms leading to different molecular driving forces, the combination of these two types of irradiation is really appealing. In the 1990s, description of the first apparatus allowing the simultaneous use of microwaves and ultrasound was reported.[47] Dedicated equipments for sequential and/or simultaneous microwave and ultrasound irradiation (SMUI) are available.[40,46,48,49] This hybrid technology is still scarcely explored to promote organic transformations and comprehensive studies are still missing. Pioneering is also the association of ultrasonic and flow reactors, already applied to scale-up the transesterification reactions of fatty acids occurring for biodiesel production.[50] Being both topics beyond the scope of this review, the readers can refer to specific literature available on these subjects.

2. Sonochemistry in aqueous solvent

Due to its intrinsic safety and environmental friendliness, water represents the obvious benchmark among green solvents. Sonochemical reactors, by analogy with the ubiquitous sonication cleaning baths, are often operated in water or aqueous solutions, since cavitation is considerably efficient (except at high temperature). In addition, the use of large volumes of solvent of negligible cost favours the scalability of the process. It is also worth noting that ultrasounds, by producing a very effective agitation and maximizing the contact between phases, facilitate to overcome the major limitation of reactants water solubility, which is particularly troublesome in organic synthesis. The examples described in this section are divided in two main parts. The first one focuses on the description of organic reactions [multi-component reactions, aldol condensations, Knoevenagel synthesis, metal-catalysed olefin transformations, etc.], where the use of water and/or ultrasound is beneficial to the outcome of the synthesis (better yields, shorter reaction times) and/or to switch the mode is able to drive the preparation of nanomaterials with different shapes (particles, flowers, flakes, rods, etc.) and size, reaction selectivity towards the target. A second section is devoted to the use of ultrasounds for the preparation of polymers or nanosystems. US irradiation compared to either (solvo)thermal conditions or on the way samples are irradiated.

2.1. Organic reactions in water phase and emulsions

Cravotto et al.[51] described the use of high-intensity ultrasounds to promote the aldol reaction between acetophenone and non-enolizable aldehydes in catalyst-free, aqueous heterogeneous systems, in one of the first remarkable paper in the field (Scheme 4). Good yields of aldol products were obtained in less than 1 h sonication time, avoiding the elimination reactions yielding enones, commonly observed in conventional conditions. Notably, a probe sonicator operating at 20 kHz and 250 W afforded faster and more selective transformations not only with respect to vigorous magnetic stirring but also to a relatively high frequency (35 kHz), low power (140 W) ultrasonic cleaning bath, highlighting the pivotal role played by the acoustic intensity of the experimental setup.

Evidences of the better performance of water over organic solvents as sonochemical medium are reported for the preparation of dihydropyrano[2,3-*c*]pyrazoles (Scheme 5a).[52] Several solvents were screened in a test reaction at 30 °C using 4-methylbenzaldehyde as substrate. While yields in methanol and ethanol (76% and 86% respectively) were only slightly lower than in water (88%), acetonitrile and less polar organic solvents such as THF and dioxane gave markedly worse results (38%, 32% and 35% yield, respectively). In this study, sonication was applied by a 250 W medical US cleaner operating at a frequency of 40 kHz, which afforded the highest reaction rate when adjusted at 50 °C. A very similar one-pot synthesis of pyrazoles was also reported by Shabalala et al.,[53] via a multi-component reaction of aromatic aldehydes, with hydrazine monohydrate and ethyl acetoacetate, in

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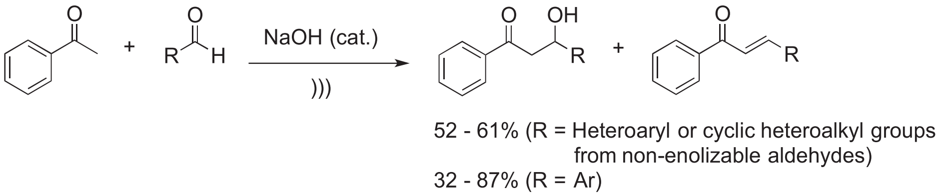
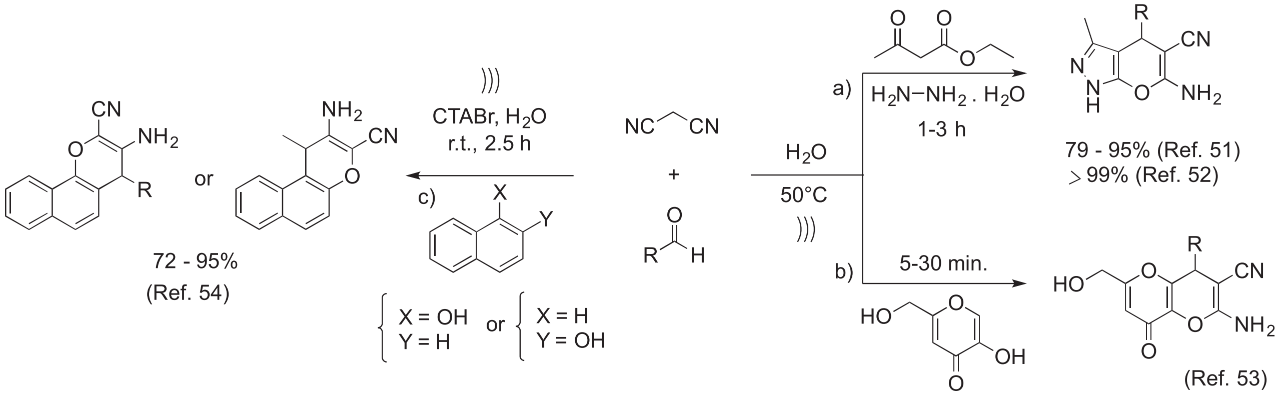


Scheme 4. Selective aldol reactions.



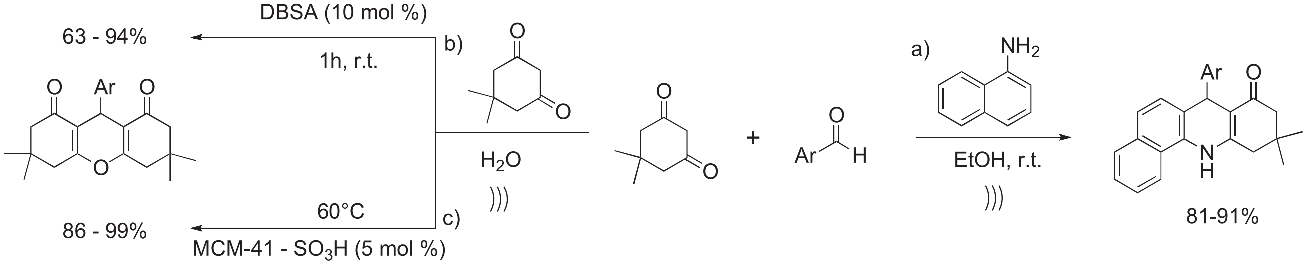
Scheme 5. Three-component reaction to dihydropyrane scaffolds in water or in emulsified conditions.

malononitrile/ammonium acetate-containing water (Scheme 5a). Traditional chromatography and tedious purification steps could be avoided, affording highly selective conversion with no formation of by-products. This reaction occurred also at room temperature, but at 50 °C, the yields were close to 100% and the reaction times were shortened in a range of 1–3 h employing the US apparatus described above.

2-Amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile scaffolds were obtained in aqueous media under ultrasound irradiation, via a transition metal and base free three-component reaction, by replacing ethyl acetoacetate by kojic acid, to afford 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile scaffolds.[54] The combinatorial synthesis was carried out in a cleaner bath (40 kHz, 200 W) in water at 50 °C (Scheme 5b). Jin et al.[55] demonstrated the efficacy of a 25 kHz, 500 W sonication bath as the energy source for the three-component reaction involving aromatic aldehydes, malonitrile and phenols, to prepare 2-amino-2-chromenes in high yields and in relatively short times (*i.e.* 2.5 h) (Scheme 5c). The authors pointed out how the combination of aqueous solvent and 10% cetyltrimethylammonium bromide (CTABr) as a phase-transfer catalyst afforded results that could not be reproduced when water was replaced by ethanol or dichloromethane, and attributed this marked solvent effect to the water-induced hydrophobic interactions between substrates and catalyst.

However, it is worth reminding that the better performance of water over organic solvents is not a general principle, and various organic transformations or experimental setups may lead to a different choice of solvent, as witnessed by the EtOH phase synthesis of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9H)-one derivatives reported by Zhang and co-workers[56] who used a 250 W cleaning bath operating at 40 kHz (Scheme 6a) or in the regioselective cyclocondensation reaction of enones with substituted phenyl hydrazines in the preparation of 1*H*-pyrazole-3-carboxylates.[57]

The same sonochemical apparatus, operating at 250 W, was employed by the same group of investigators to improve the synthesis of 1,8- octahydroxanthene and its derivatives in the aqueous phase, with *p*-dodecylbenzensulfonic acid (DBSA) as catalyst[58] (Scheme 6b). A comparison with the conventional water reflux heating procedure demonstrated a significant reaction improvement under US irradiation, from 63% yield in 3 h–94% yield in only 1 h. By analogy with their previous study, it is interesting to notice how water has been reported to outperform any other organic solvent (*i.e.* ethanol, trichloromethane and cyclohexane) in the described experimental conditions. The same reaction was studied by Rostamizadeh and co-workers[59] in heterogeneous conditions using zeolites (Scheme 6c). The synthesis of 1,8-dioxo-octahydroxanthene derivatives could be carried out at 60 °C under



Scheme 6. Ultrasound-promoted cyclocondensation reaction via a Knoevenagel intermediate.

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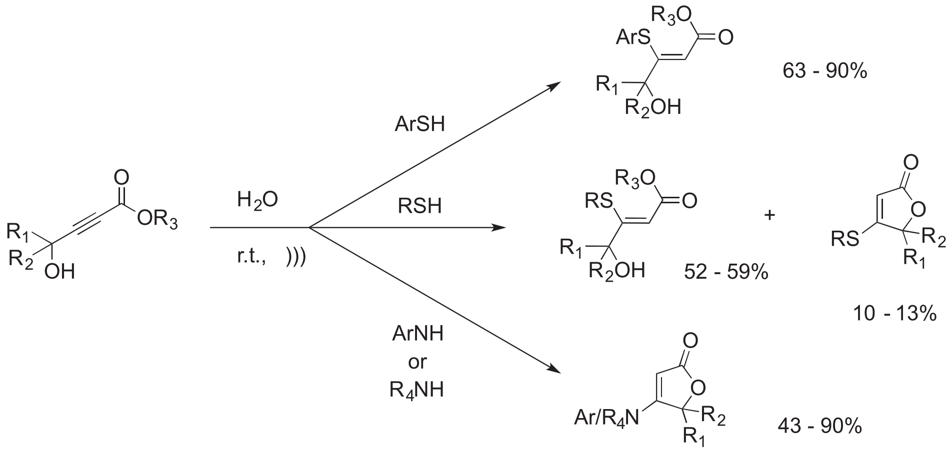
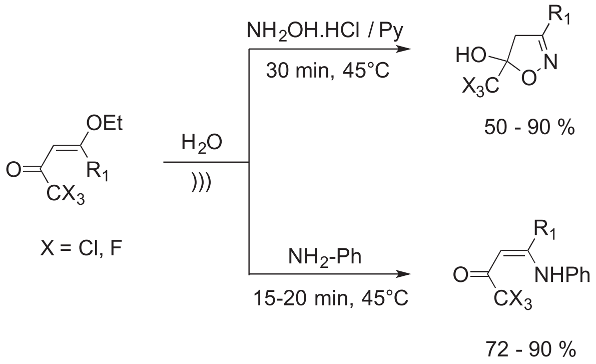


Scheme 7. Michael addition of thiols or amines.

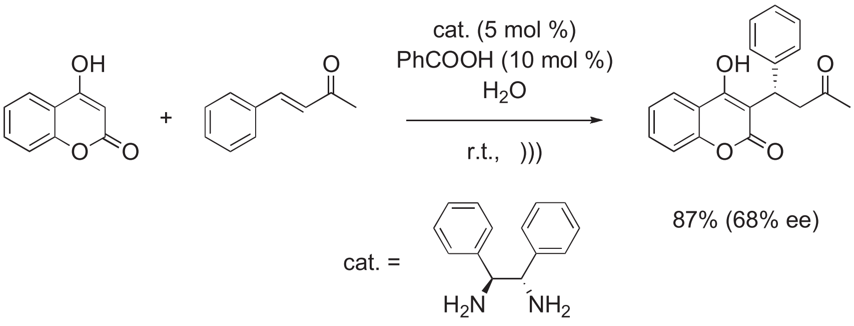
sonochemical conditions (25 kHz frequency), in 80%–99% yields, from aromatic aldehydes and dimedone (5,5-dimethyl-1,3-cyclohexanedione). In the absence of US irradiation, the reaction did not progress (moderate yields were attainable only by raising the temperature to 90 °C). This was explained by the synergistic effect between ultrasonic waves and the nanostructured catalyst MCM-41-SO_3H, resulting in a localized intense pressure derived from cavitation, and promoting the insertion of reactants into the sulfonic group functionalized channels of the porous material.[59]

Neutral aqueous solvent compared favourably with acetonitrile in the US-promoted Michael addition of thiols to 4-hydroxy-2-alkynoates, using a sonication bath at room temperature.[60] The beneficial role of water was suggested to arise from the hydrogen bond interaction with both the carbonyl oxygen and the thiol group. Indeed, in acetonitrile proceeded in similar yields only in the presence of $NaHCO_3$ as an additional base. When amines were employed as substrates instead of thiols, a sequential conjugate addition/lactonization reaction led to amino-furan-2-ones (Scheme 7). In these conditions, a test in water without sonication revealed a significant, albeit not dramatic decrease in the reaction rate.

The Michael addition was also the key step for the sonochemical synthesis (cleaning bath) of the anticoagulant (*S*)-warfarin from 4-hydroxycumarin and benzylidene-acetone, utilizing commercially available (*S,S*)-diphenylethylenediamine as catalyst (5 mol %) and benzoic acid (10 mol %) as an additive (Scheme 8).[61] The synthesis was achieved by an ‘on water’ procedure in which the aqueous phase remained separated from both reactants and the product, which are insoluble and react on the surface of the solvent and then precipitate spontaneously. This strongly facilitated the workup and purification steps in terms of operational simplicity and reduction of solvent utilization (simple filtration and recrystallization from hexane were needed). It is underlined by the authors that, in order to reach a high efficiency, an ‘on water’ reaction needs appropriate contacts between reactants and, hence, vigorous agitation. Indeed, a three-fold increase in the warfarin yield was observed in preliminary tests, by replacing intense mechanical stirring with an ultrasonic cleaning bath. Moreover, the reaction was repeated scaling up the synthesis from 0.50 to 5.0 mmol of 4-hydroxycumarin under otherwise identical conditions. As a result, a lower yield (55%) and a higher enantiomeric excess (>99%) were observed, although this variation was neither commented nor explained in the paper. It was also possible to recycle the aqueous phase containing the catalyst at least three times without loss in



Scheme 9. Preparation of trihalomethyl-substituted dihydroisoxazoles and β-enamino ketones.



Scheme 8. Organo-catalysed “on-water” Michael addition for the preparation of the anticoagulant (*S*)-warfarin.

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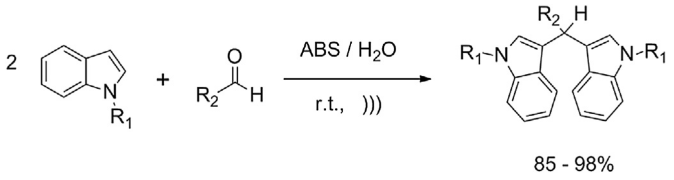


Scheme 10. Ultrasound outperforms for the addition reaction of indoles to aldehydes.

efficiency in terms of yields (95%) and selectivity (>99%).[62]

The accelerating effect of ultrasound was also demonstrated for the preparation of trihalo-substituted dihydroisoxazoles and β-enamino ketones, upon irradiation with a titanium microtip[63] (Scheme 9). The 1,1,1-trihalo-4-alkoxy-3-alken-2-ones reacted with hydroxylamine and aniline in shorter the reaction time (15–30 min) compared to conventional methods (16–20 h), leading to similar yields.

Ultrasound activation was also beneficial for the aqueous phase preparation of bis-(indolyl)-methane derivatives in the presence of dodecylbenzenesulfonic acid (ABS) as catalyst and emulsifier (Scheme 10).[64] A four-fold rate enhancement, with respect to 'silent' stirring was registered, with identical results when the 250 W cleaning bath was set at two different operational frequencies (*i.e.* 25 kHz or 40 kHz), which is a rarely investigated parameter. The same reaction was previously carried out in analogous conditions (aqueous phase; 35 kHz, 200 kW sonication bath) and with similar results employing 10 mol% of 1-hexenesulphonic acid sodium salt as catalyst.[65]

The addition of aromatic aldehydes to acetyl acetone derivative and thiourea at room temperature was also applied to prepare a series of pyrimidine derivatives under ultrasound irradiation in aqueous NaOH solution (Scheme 11).[66] In particular, in a more concentrated NaOH solution (1 equivalent), sonication noticeably reduced the reaction times and increased the yields of the reaction products (from 75 to 90%). US source was a cleaning bath operating at 40 kHz under a nominal power of 250 W. Worthy to mention is the particularly easy and fast work-up.

The catalyst-free Biginelli reaction was also studied by Suman et al.[67] who demonstrated the pivotal role of water when thermal conditions (reflux), microwaves or ultrasounds were used to prepare 3,4-dihydropyrimidinones. As a result, while comparable yields were obtained independently on the activation technique that was used, shorter reaction times were possible under microwave- (2 min) or ultrasound- (30 min) promoted reactions. The use of a 1:1 mixture of water with other polar protic solvents (MeOH, EtOH or *i*-PrOH) resulted in lowering yields, even for extended reaction times. The authors claimed that water favoured formation of the acylimine intermediate (rate determining step) by interaction of the aldehyde and the urea through hydrogen bonding. This effect was less pronounced when other protic solvents were present.

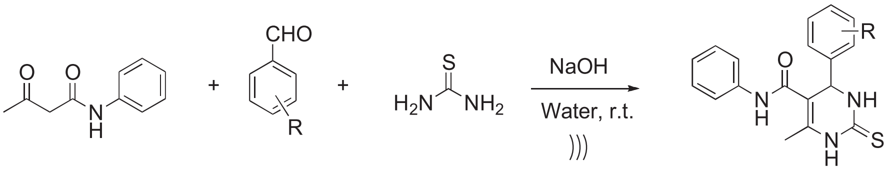
A copper-catalysed four-component reaction starting from a solution of phenylhydrazines, ethyl acetoacetate, substituted aromatic aldehyde and β-naphthol in water, in the presence of nanosized CuI as catalyst, afforded several substituted pyrazolones with yields higher than 90% (Scheme 12). Sonication clearly reduced the reaction time to 30–45 min compared to thermal (refluxing conditions, 6–7 h) reactions. Sonication was performed by a multiwave US generator equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz and a power of 50 W.[68]

Highly substituted propanamide derivatives were also prepared in water by a catalyst-free, one-pot procedure via isocyanide-based three component reactions, and were recovered pure without further treatment (Scheme 13).[69]

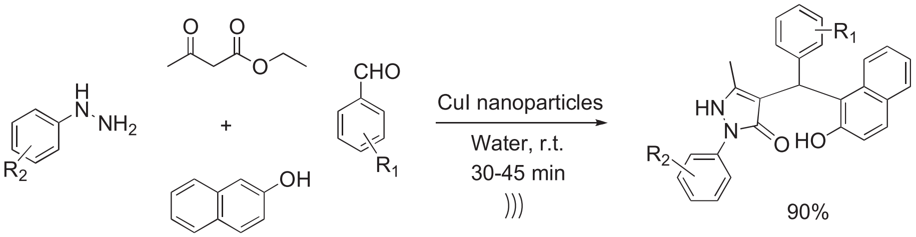
It was demonstrated that not only ultrasound activation led to improved yields and shorter reaction times (40 min reaction) compared to conventional 'silent' conditions under reflux (24 h reaction), but that the use of water outperformed instead of other organic solvents (DMF, THF, CH_3CN or 1,4-dioxane), affording poor conversion of substrates.

Hydrotropes are amphiphilic molecules with hydrophobic moieties too short to induce micellization in aqueous media. They maximize hydrophobic interactions with organic molecules and provide an outstanding solubilizing power. With this purpose, sodium *p*-toluenesulfonate (NaPTS) was employed in the sonochemical synthesis of β-aminocarbonyl compounds in water (40 kHz, 100 W sonication bath kept at room temperature) (Scheme 14).[70] On the basis of a model reaction using acetophenone, aniline and benzaldehyde, the authors underlined the crucial importance of the hydrotrope concentration, observing a peak of activity with a 50% (w/w) aqueous solution (Fig. 4). They reported that in the absence of sodium *p*-toluenesulfonate or in 'silent' conditions, the synthesis gave considerably lower yields (*i.e* 75% vs. 90% yield for the model reaction of acetophenone with aniline and benzaldehyde). β-Aminoketones could also be synthesized by an US-assisted Mannich reaction in water, in the presence of bismuth(III) triflate: high yields with *anti* selectivity were obtained within 1–2 h at room temperature.[71]

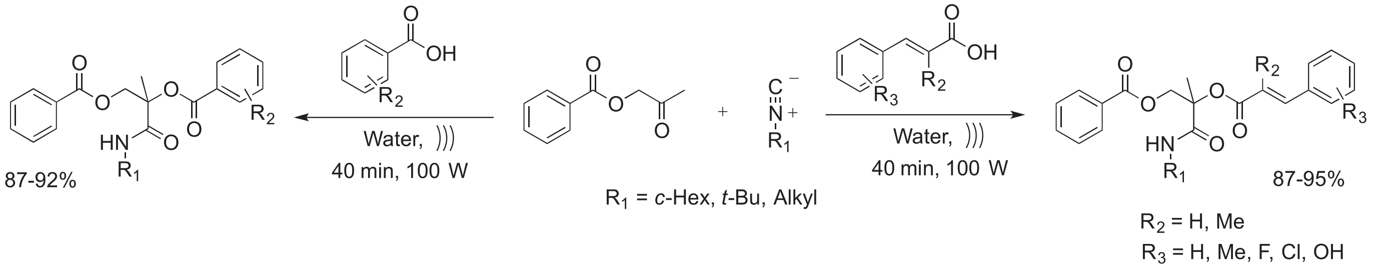
Finding the optimal reaction set-up may require many attempts, and yield increase in sonochemical conditions cannot be taken for granted. As a recent example, the squaric acid catalysed-synthesis of *N*-phenyl-pyrrole in water[72] proved to be more efficient under conventional thermal heating (95% yield at 60 °C) than in the presence of ultrasounds (70% yield with a 250 W Hielscher *Vial Tweeter*) (Scheme 15). The same group of investigators reported that 2-hydroxy-dithiocarbamates were formed from amines, epoxides and carbon disulphide in very short times of 7–10 min, employing the same sonicator equipped with a sonotrode (Scheme 16).[73] Interestingly, the authors monitored the effect of the US output amplitude observing an increase in 2-hydroxy-dithiocarbamate yields with the increase of amplitude (50%, 60% and 80% amplitudes gave, respectively, 60%, 80% and 95% yields). Moreover, a model reaction with pyrrolidine and phenyl glycidyl ether (95% yield in water) was carried out in a choline chloride-based deep eutectic solvent and liquid, low molecular weight liquid PEG. Slightly lower yields of 80% and 82% respectively were obtained and the use of these two alternative solvents, which are seldom coupled with sonication, was not further discussed in the paper.



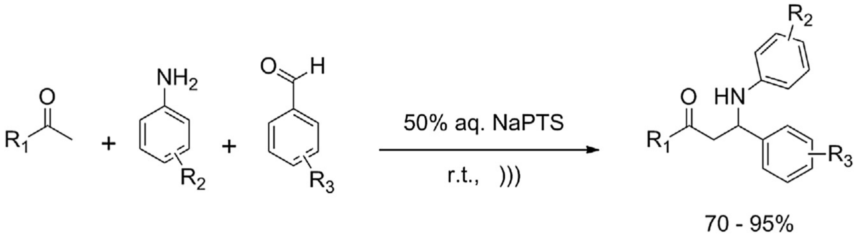
Scheme 11. Biginelli-type preparation of dihydrothiopyrimidines.



Scheme 12. Copper-mediated synthesis of pyrazolones by multi-component reaction.



Scheme 13. Aqueous Passerini-type reaction under sonication.



Scheme 14. Hydrotrope concentration drives the preparation of β-aminocarbonyl compounds in water.

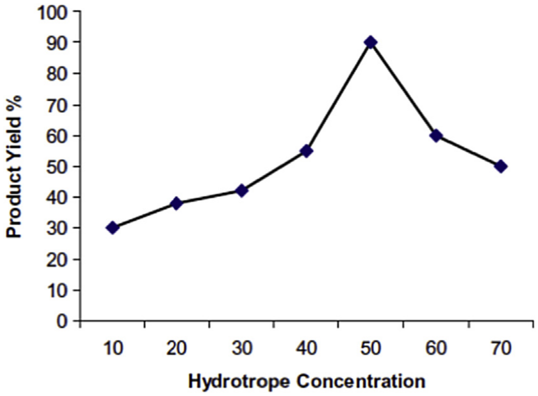
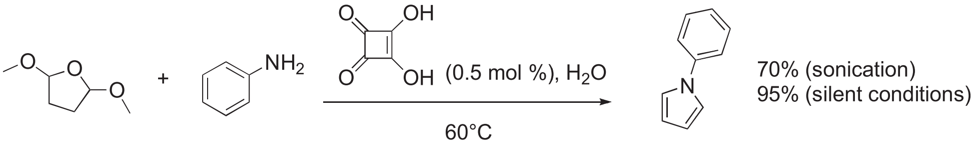


Fig. 4. Yield of the β-aminocarbonyl compound obtained from acetophenone, aniline and benzaldehyde at different sodium *p*-toluenesulfonate concentration in water (Image reproduced from reference 54, by kind permission of Elsevier).

Eventually, although the solvent system is not entirely ‘green’, it is worth reporting that US-irradiation (using a probe reactor) was employed in place of a pillared clay phase-transfer agent to carry out the reaction between α-tosyloxyketones contained in the organic phase (chloroform or acetonitrile) and sodium azide contained in water (Scheme 17).[74]

Recently, Oget and his group[75] showed that the $RuCl_3/NaIO_4$-catalysed oxidative cleavage of several olefins could be carried out in water instead of previously utilized water/organic solvents systems, provided that a sonochemical microprobe reactor (20 kHz; 130 W) was employed in the presence of an emulsifier (namely, Aliquat® 336) (Scheme 18). In a test with 2% catalyst and 1-decene as a model substrate, conversion increased from 27% to 99% after 20 min when magnetic stirring was replaced by ultrasonic irradiation. Nonetheless the reported yields remained lower than those obtained by means of the standard biphasic systems.

The rate of Pd–catalysed Heck coupling of aryl iodides with



Scheme 15. Ultrasound *vs.* silent conditions for *N*-aryl-pyrroles preparation.

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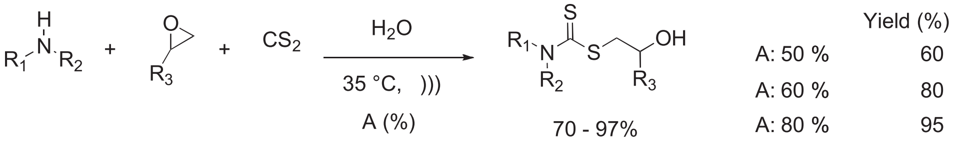
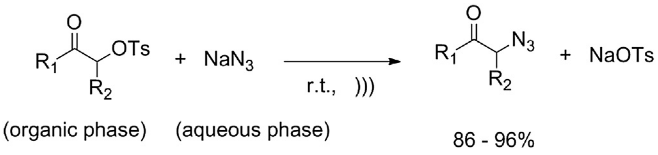


Scheme 16. Synthesis of thio-carbamates.



Scheme 17. Biphasic substitution reaction.

activated olefins in the presence of sodium dodecane-1-sulfonate showed a marked dependence on temperature (Scheme 19).[76] A probe sonicator was coupled with oil bath heating, in order to enhance the yield of cinnamamide from 35% (at 40 °C) to 47% (at 60 °C) to 96% (at 90 °C). According to the authors, however, the sonochemical enhancement was evident since, employing 5 mol % $Pd(OAc)_2$ and K_2CO_3 as the auxiliary base, reactions with >99:1 selectivity towards the *E* isomer could be completed within only 20 min. Efficient pyrrole and pyridazine sonochemical syntheses in aqueous solvent were also reported in recent papers[77,78] in which advantages like increased reaction rates, operational simplicity and the absence of added catalyst were highlighted.

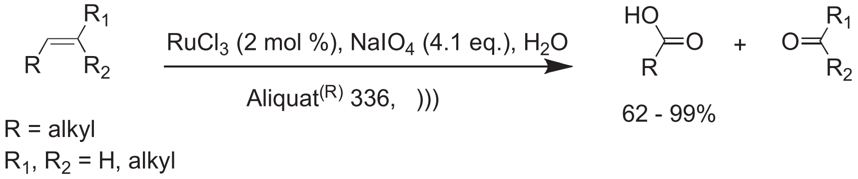
2.2. Polymerization, reticulation reactions and composite material preparation

Ultrasounds were employed to promote polymerizations since a relatively long time, taking into account the formation of radical species during cavitation. A remarkable example of sonochemical styrene polymerization in water/sodium dodecyl sulphate (SDS) emulsion (Fig. 5), has been described by Biggs and Grieser in 1995 (20 kHz probe reactor with 10–20 W/cm^2 intensity).[79]

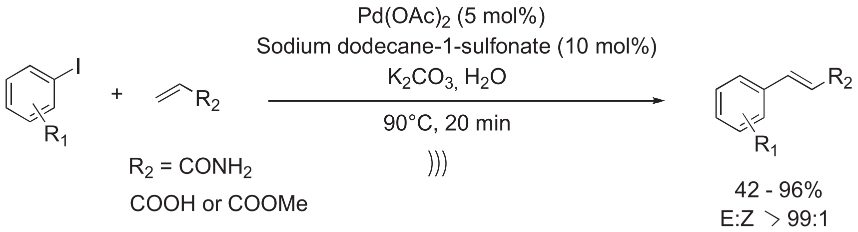
A few years later Fujiwara and co-workers[80] described the synthesis of poly(vinyl chloride)-*block*-poly(vinyl alcohol) (PVC-*block*-PVA) copolymers resulting from the US-induced poly(vinyl chloride) (PVC) and polyvinyl-alcohols (PVA) homopolymers (150 W, 25 kHz probe) (Fig. 5b and c) by chain scission and recombination of free radicals formed on the end groups of the blocks (Scheme 20). A fast reaction rate (92% conversion after 11 min) was observed for the emulsion polymerization of *n*-butyl acrylate (Fig. 5d) when sonication (20 kHz probe reactor) was used to initiate the radical mechanism instead of a conventional, thermally activated chemical initiator.[81] In a very thorough study, the authors investigated the process of radical formation, and highlighted the marked reduction of polymerization induction time and the higher molecular weight attainable under US irradiation. Moreover, the feasibility of semi-continuous and continuous syntheses to replace batch reactions for larger scale purposes was demonstrated. Here, emulsions were formed in the presence of sodium dodecylsulfate (SDS). The presence of an amphiphilic additive was not necessary in the US-enhanced random copolymerization of styrene and acrylic acid (Fig. 5e) initiated by azobisisobutyronitrile (AIBN), as described by the group of Yan.[82]

US irradiation (20 kHz, 6 mm tip diameter probe) in water provided the required emulsification effect, and reduced the induction time, by facilitating mixing between co-monomers and the initiator. The authors investigated the effect of the US power output on the copolymerization rate and a dramatic increase in conversion (*i.e.* 85% vs. 25% after 30 min of reaction) was observed when the power density was tuned up from 0.12 to 0.23 W/cm^3. This power density variation produced a marked decrease (from c.a. 90 to 55 mL/g) in the characteristic viscosity of the styrene/acrylic acid copolymer, suggesting that the more vigorous shear forces induced a partial degradation of the polymer chains.

Emulsifier- and initiator-free polymerization of a butyl acrylate/styrene/acrylamide mixture performed with a sonochemical probe in aqueous phase gave ternary copolymer (Fig. 5f), nanoparticles with a smaller size than that observed in the corresponding silent conditions (*i.e.* 80 nm vs. 140 nm).[83] The sonochemical polymerization was faster than the corresponding conventional procedure, while the maximum monomer conversion achieved was somewhat lower. Indeed, 65% conversion after 1.5 h was obtained under US



Scheme 18. Ruthenium-catalysed oxidative cleavage of olefins.



Scheme 19. Selective syntheses of *E*-olefins by palladium-catalysed Heck reaction in emulsified water.

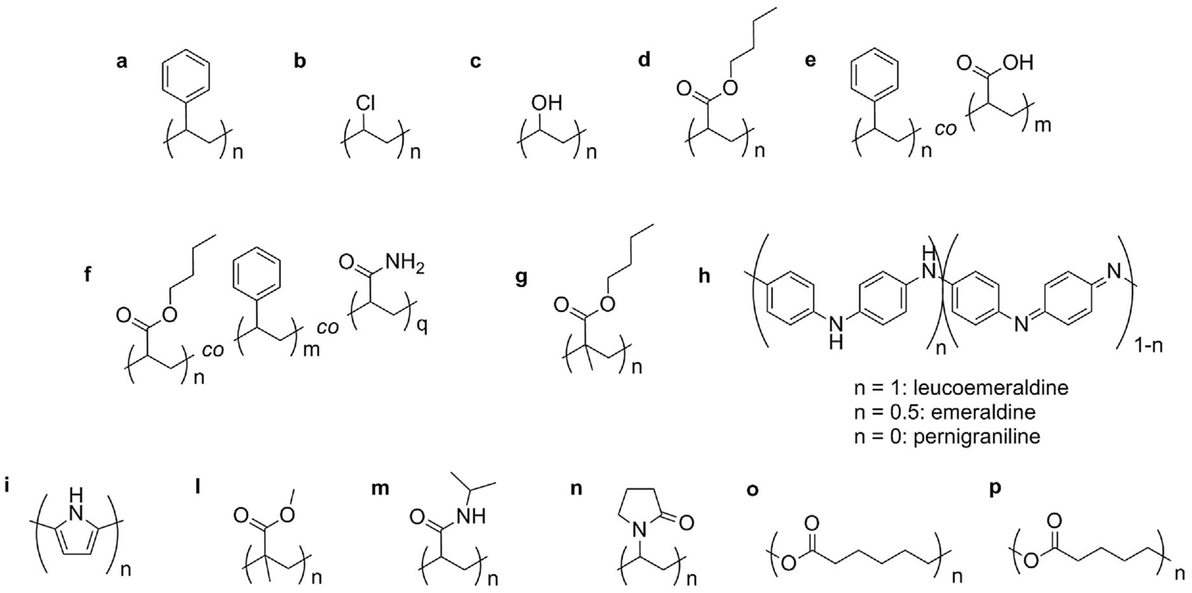
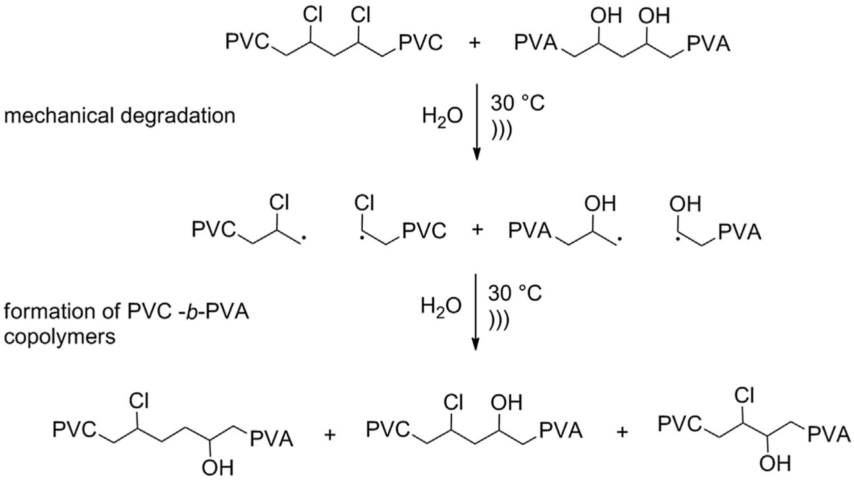


Fig. 5. Structure of poly(styrene) (**a**), poly(vinyl chloride) (**b**), poly(vinyl alcohol) (**c**), poly(*n*-butyl acrylate) (**d**), styrene/acrylic acid copolymers (**e**), *n*-butyl acrylate/styrene/acrylamide copolymers (**f**), poly(*n*-butyl methacrylate) (**g**), poly(aniline)s (**h**), poly(pyrrole) (**i**), poly(methyl methacrylate) (**l**), poly(*N*-isopropyl acrylamide) (**m**), poly(vinyl pyrrolidone) (**n**), poly(ε-caprolactone) (**o**) and poly(δ-valerolactone) (**p**).



Scheme 20. Ultrasound-promoted synthesis of block-copolymers.

irradiation, compared to 80% conversion after 3.5 h under stirring, after prolonged US irradiation conversion remained stable. The authors found that a maximum in monomer conversion was observed operating the US probe at an acoustic intensity of about 9.5 W/cm^2. Moreover, the addition of Na_2SO_4 was required for the continuity of the reaction, although the concentration of inorganic salt had roughly no influence on the rate of monomer conversion. According to the authors, this finding could be explained on the basis of two contrasting effects: the salt was responsible for the formation of an electric double layer on the nanoparticle's surface preventing aggregation phenomena, while an excessive concentration compressed the double layer destroying the emulsion.

More recently, the mini-emulsion polymerization of *n*-butyl methacrylate (BMA) (Fig. 5g) was carried out under mild sonochemical conditions (probe reactor operating at 20 kHz and 8 W/cm^2) in water, in the presence of SDS as surfactant. The reaction was completed within 20 min of irradiation at room temperature, yielding a polymer of high molecular weight of approximately 3 × 10^6 g/mol, with no comparison with a conventional procedure.[84] The authors emphasized that mini-emulsions produced by sonication did not require a hydrotrope, commonly used in conventional mini-emulsion preparations. Moreover, the addition of organic liquids (in which the monomer is soluble) to the water/SDS mixture, produced a reduction in the polymerization rate and extent, which was particularly marked when aromatic hydrocarbons were added. As an example, the addition of toluene lowered the poly *n*-butyl methacrylate molecular weight to about 1 × 10^6 g/mol, with little variation (1%–25%) of the volume. These results may derive from solvency and steric effects, although it was pointed out in that a theoretical rationalization was not straightforward.

High-intensity sonication (20 kHz, 100 W/cm^2 probe reactor) of copper(II) acetate in a water solution containing aniline (1% vol.) yielded composite materials in which nanocrystalline Cu_2O particles were embedded in a poly(aniline) (PANI) matrix (Fig. 5h).[85] It was hypothesized that after reduction to Cu(0), partial re-oxidation was due to the formation of H_2O_2 or other secondary species originating from the recombination of H• and OH• radicals. Accordingly, when the reaction was performed in pure aniline as solvent, Cu(0) nanoparticles were obtained. It was pointed out that particles synthesized in pure aniline were amorphous. This finding may be rationalized, considering the higher temperature gradients and quenching rates generated from sonication of a solvent with a lower vapour pressure than water. In a further study on US-induced aniline polymerization (100 W, 50 kHz sonication bath), conducting PANI nanofibers with diameters of around 50 nm and micrometer-scale lengths were synthesized from an HCl solution containing the monomer to which ammonium persulfate (APS) as the oxidant was slowly added.[86] As expected, increasing initial amounts of oxidant produced shorter fibers; moreover, it is worth noting that the same procedure carried out under mechanical stirring yielded irregular, micro-sized PANI particles derived from the aggregation of growing nanofibers.

A silver nanowire/PANI (emeraldine salt) composite was obtained by sonication of an aqueous solution of silver nitrate and anilinium nitrate, at room temperature, by means of a non-specified home-made US equipment operating at 50 W/cm^2 acoustic intensity and at an unusually high frequency of 475 kHz.[87] The role of added isopropyl alcohol was accurately discussed, highlighting the beneficial effects on the silver wire's properties and the dispersion stability. Apparently, the alcohol also acted as a scavenger for the OH• radicals generated by sonication in water and, hence, slowed down the aniline polymerization kinetics. In other examples of PANI or polypyrrole-based composites, sonication was carried out during polymerization with the main goal of preventing aggregation of the nanosized charges. A conducting PANI (emeraldine salt) nanocomposite containing preformed Y_2O_3 nanoparticles was also prepared adding the monomer, followed by the metal oxide into a diluted [HEMIM][H_2PO_4] aqueous solution.[88] Sonication was applied with a probe system (100 W, 40 kHz) only after 1 h stirring to better disperse Y_2O_3. With a similar approach, the synthesis of graphene containing PANI and polypyrrole (Fig. 5i) composites required US irradiation by a probe reactor during the initial phase, to optimize the dispersion of graphene or modified graphene sheets in the CTABr containing aqueous solvent.[89]

For application in gas-sensing field, a uniform dispersion of $ZnMoO_4$ nanoparticles in PANI matrix improved the physical and chemical properties of PANI-based polymers. An innovative strategy was developed by the Bhanvase research group[90] which used an ultrasound-assisted synthetic protocol using different loading $ZnMoO_4$ nanoparticles (Fig. 6).

For a better compatibility with PANI, the $ZnMoO_4$ nanoparticles were functionalized using myristic acid. The cavitation effects induced by ultrasonic irradiations showed significant enhancement in the dispersion of functionalized zinc nanoparticles into the PANI during the US-assisted *in-situ* emulsion polymerization process. TEM images of PANI/$ZnMoO_4$ nanocomposite particles gave a direct evidence of fine dispersion and encapsulation of fatty acid stabilized $ZnMoO_4$ nanoparticles inside the PANI matrix.[90]

For the preparation of conductive polypyrrole dispersions,[91] instead of trying to enhance the pyrrole polymerization rate, and with the aim of increasing conductivity compared to the much larger (368 nm average diameter) and more broadly distributed particles synthesized by mechanical stirring, an US probe reactor was used to obtain small polymer particles (*i.e.* 67 nm average diameter).

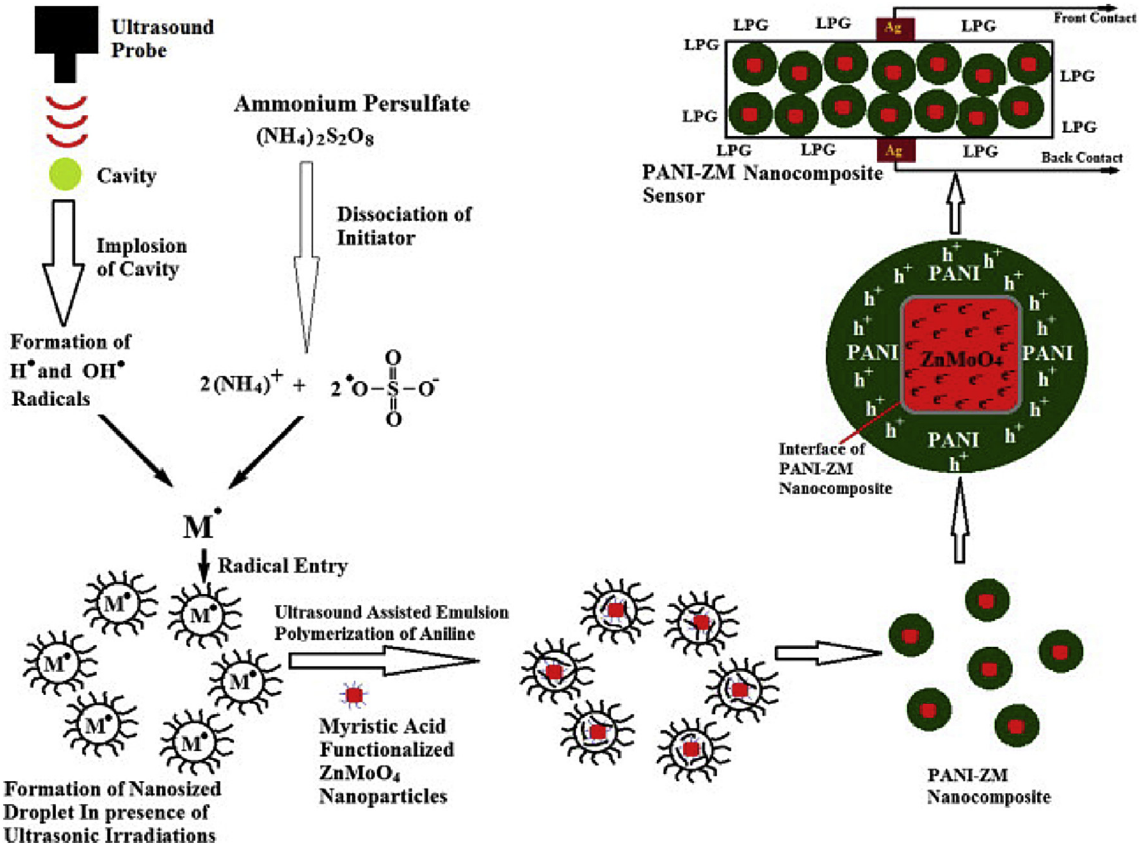


Fig. 6. Mechanism of formation of PANI/$ZnMoO_4$ nanocomposites by US *in situ* emulsion polymerization and model for PANI/$ZnMoO_4$ nanocomposite's sensor mechanism (Image reproduced from reference 74, by kind permission of Elsevier).

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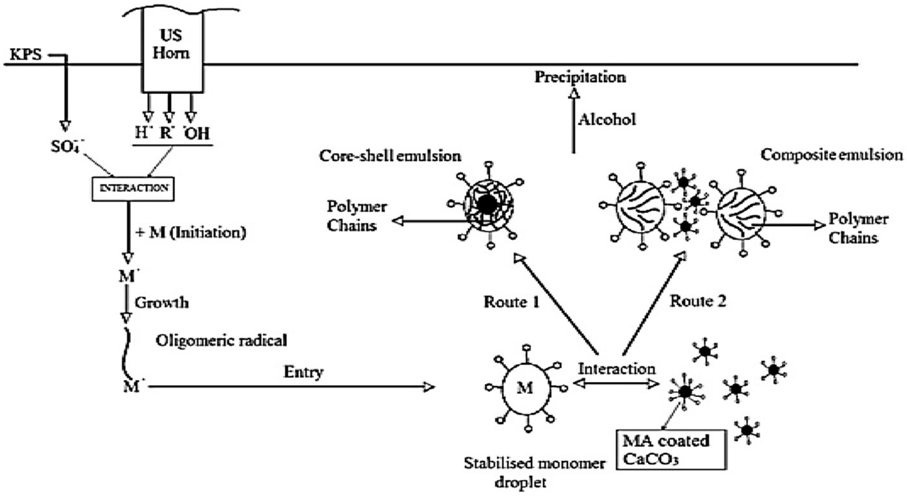


Fig. 7. Sonochemical synthesis of PMMA/$CaCO_3$ systems (Image reproduced from reference 76, by kind permission of Elsevier).

The combined US (20 kHz probe sonicator)/potassium persulfate (KPS) initiation of methyl methacrylate (MMA) polymerization (Fig. 5l) proved to enhance the final conversion with respect to each of the two methods alone and allowed the synthesis of PMMA/$CaCO_3$ systems with narrow particle size distributions (Fig. 7).[92] On the other hand, combined initiation unexpectedly lowered the initial polymerization rate compared to the non-sonochemical process. This finding may be explained by the interfering reactivity between the highly unstable $SO_4^{\bullet -}$ radical anion and the radicals generated from the water sonolysis.

On the contrary, a considerable speed up of the poly(methyl methacrylate-*co*-butyl acrylate) polymerization rate was observed when ultrasound was applied with a 22 mm standard titanium probe. In fact it was reported that ultrasound pulses in the first minutes of polymerization increased instant free radical to monomer ratio, as well as mixing efficiency, which led to higher monomer conversion, improved polymerization and remarkable decrease in molecular weight distribution. Particle size and particle size distribution were significantly affected, particle size decreased, and more uniform particles were obtained (Fig. 8).[93]

Mesoporous silica nanoparticles functionalized with 3-(trimethoxysilyl) propyl methacrylate were grafted with poly(*N*-isopropyl acrylamide) (PNIPA) (Fig. 5m) using an ultrasound induced (40 kHz cleaning bath) emulsion polymerization initiated by potassium persulfate (KPS) in the presence of CTABr (Scheme 21).[94] The obtained nanocomposites were characterized by a core-shell structure with an average diameter of 170 nm. They demonstrated promising pH sensitivity, biocompatibility and bactericidal activity. It is highlighted by the authors that the obtained PNIPA-grafted nanoparticles showed an enhanced biocompatibility, compared to the previously described PNIPA hydrogels or PNIPA coated nanoparticles obtained with no US irradiation. Furthermore, the proposed sonochemical synthesis required neither additives, like cross-linkers, nor hydrophobic agents, organic solvents, which were necessary for many conventional techniques in the field of nanocomposites.

Panigrahi and Srivastava[95] focused their studies on the preparation of uniform hollow polyaniline microspheres by US-assisted polymerization of aniline monomers, selecting polystyrene spheres as templates that were used to develop hollow sphere polyaniline/Ag nanocomposites. The electrical conductivity of materials was found to be higher than the polyaniline hollow microspheres obtained by conventional routes, and furthermore they successfully used these microspheres as sensors and as an effective catalyst in the reduction of 4-nitrophenol.

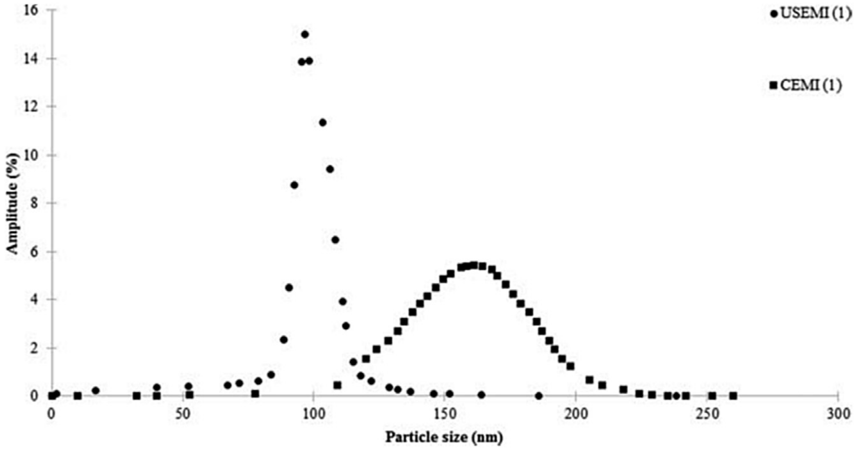
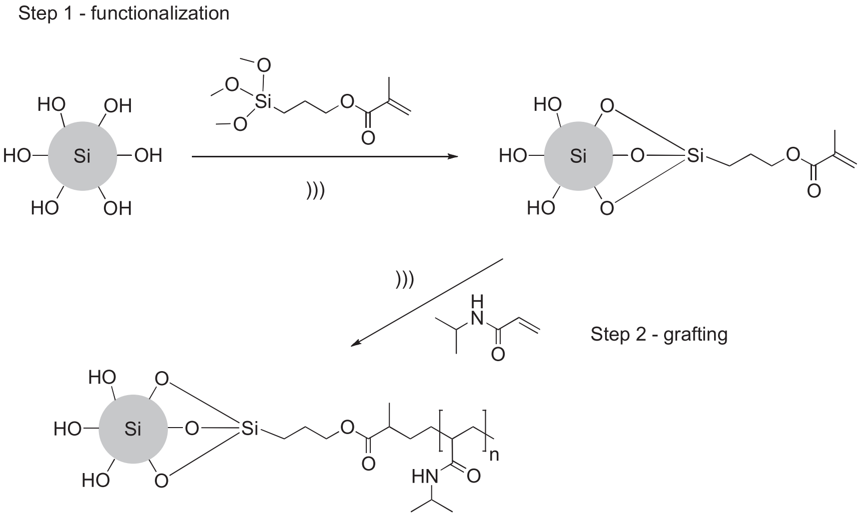


Fig. 8. Dynamic light scattering results of ultrasound and conventional polymerization of poly(methyl methacrylate-*co*-butyl acrylate) (US: cycles; conventional: squares) (Image reproduced from reference 77, by kind permission of Wiley).



Scheme 21. Mesoporous silica nanoparticles grafted with PNIPA polymer.

2.3. *Synthesis of metal nanoparticles and nanomaterials*

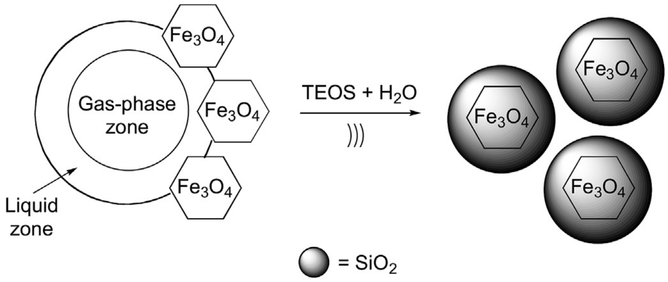
Nanomaterials are an increasingly important class of compounds that have revolutionized everyday life. They are used, above all, in healthcare, electronics, cosmetics and many other basic and important areas. Their physical and chemical properties often differ from those of bulk materials, so they can have new an unthinkable use that are changing our life. Among the several synthetic strategies to produce them, ultrasounds offer a simple and efficient route that can be exploited to achieve control over growth. Parameters such as type of solvent, ultrasound frequency and power can be modulated to obtain a nanomaterial having the desired characteristics.[27] In particular, sonochemistry allows a fine control over the crystallinity that enables synthesis of amorphous metals and metal alloys. Furthermore, the cavitation formed during the sonochemical processes provide unique interactions between matter and energy, being the temperature inside the hot spots >5000 K, pressure higher than 1000 bars and cooling rate extraordinarily elevated (10^{10} K s^{-1}). Such conditions allow to obtain a variety of new and unusual nanostructurated materials, not accessible by conventional methods. Indeed, nanocatalytic systems are usually very dynamic and involve aggregation and dissociation of the nanoparticles.[96] The success or the failure of the nanostructured material synthesis will depend upon how they are prepared.

Gold colloids are the cardinal and most thoroughly studied nanosystems. Indeed, their sonochemical synthesis from $HAuCl_4$ in different solvents such as ethanol/water (1:1 v/v) or ethylene glycol (EG) was reported by the group of Cai, already in 2003.[97] The authors underlined the dependence of nanoparticle's morphology on the reaction solvent and related this finding to the different Au(III) reduction rates. Sonication was performed at 0 °C in the presence of poly(vinyl pyrrolidone) (PVP) (Fig. 5n) as a stabilizing agent by means of a 60 W, 40 kHz cleaning bath, applying a relatively low acoustic intensity of 2.4 W/cm^2. The interest in this field has not faded with time and, recently, spherical gold nanoparticles with a relatively narrow size distribution (10 ± 1 nm) were synthesized within short sonication times (around 5 min) by means of a probe reactor.[98] The use of aqueous sodium citrate dihydrate as a green reducing agent, as well as of mild reaction conditions makes the process environmentally favourable.

The biomedical use of Au nanoparticles, which are introduced into cells for imaging or to deliver treatments, requires the use of green synthesis routes based on biocompatible processes. Accordingly, plant extracts, like a geranium leaf extract, was used as a reducing and stabilizing agent in a sonocatalysis process based on high-power ultrasounds. The synthesis proceeded within 3.5 min only, in aqueous solution, at room temperature using, a high-power US generator equipped with a 1.27 cm diameter titanium tip operating at 20 kHz with a maximum output power used never over 36 W.[99]

Among the early works, SnO_2/CdS core-shell structures were obtained by US irradiation of a neutral aqueous solution containing cadmium chloride, thiourea and preformed SnO_2 nanobelts, under Ar atmosphere.[100] The preformed nanobelts utilized as support for nanoparticles were 30–200 nm wide and 10–50 nm thick, while the synthesized CdS nanoparticles were nearly spherical, with diameters in the range of 10–20 nm. Nanoparticle's formation was completed within 3 h employing a 100 W, 40 kHz high-intensity probe sonicator.

In recent past, the significance of US enhancement was emphasized for the synthesis of monodisperse magnetite nanoparticles by oxidation of $Fe(OH)_2$ precipitate (the so-called ‘green rust’) since, in the heterogeneous mixture, the dissolution of iron ions was greatly accelerated by the microjet effect of sonication (16 W/cm^2 probe reactor).[101] In this study, the addition of ethanol to the aqueous phase had beneficial consequences on the reaction efficiency. The authors rationalized this finding on the basis of ethanol decomposition during cavitation, which resulted in an increased concentration of the radical species responsible for Fe(II) oxidation. While an ethanol/water volume ratio of 20/80 proved to



Scheme 22. Sonochemical synthesis of monodisperse Fe_3O_4-SiO_2 core-shell nanoparticles.

be the optimal solvent, a higher ratio of ethanol (*i.e.* 50/50 v/v) hampered the reaction due to the reducing properties of the alcohol. An analogous preparation was carried out either in water/di(ethylene glycol) (DEG) or water/tri(ethylene glycol) (TEG) mixtures, by means of a 100 W, 22.5 kHz probe sonicator, obtaining hydrophilic magnetite particles with low size distribution and a degree of crystallinity proportional to the DEG or TEG/water ratio.[102] Reaction involving pure EG and its polymers will be detailed later on in this review (Paragraph 4).

The solvothermal procedure in the same experimental conditions yielded an amorphous phase, while increasing the temperature from 25 to 50 °C led to unsatisfactory non-homogeneous aggregates of particles. Monodisperse Fe_3O_4-SiO_2 core-shell nanoparticles could also be obtained by co-precipitation of Fe(II) and Fe(III) in aqueous solution, followed by alkaline hydrolysis of tetraethyl orthosilicate (TEOS) in an ethanol/water mixture (Scheme 22).[103] When both steps were performed under power US irradiation (20 kHz, 30 W/cm^2 probe reactor), smaller size (around 6 vs. 10 nm average diameter), and narrower size distribution of magnetite particles as well as higher homogeneity of the silica coating, were achieved. As a result, a higher magnetization value of magnetite particles compared to those prepared under silent conditions was observed.

Iron oxide nanomaterials were synthesized from iron sulphate, by exposure to ultrasounds in combination with nitric acid addition, during precipitation of the resulting iron salt with sodium hydroxide. To predetermine the shape of the particles, the technique of natural ageing was used. Nano octahedral particles, in the range of 80–120 nm, were obtained. In addition, a study demonstrating the influence of the particles' magnetic properties was carried out.[104] An interesting application in remediation of chlorophenols was developed by Zhao,[105,106] who prepared two bimetallic catalysts consisting of either nickel or palladium decorated iron-core. 2,4-Dichlorophenol was always efficiently dechlorinated to phenol employing both Ni/Fe and Pd/Fe nanoparticles. The use of ultrasounds during the synthetic procedure (US elutriation apparatus, 20 kHz and 150 W) contributed to generate a nanomaterial with enhanced catalytic properties versus the de-chlorination reaction.

Other noteworthy examples of spherical particle synthesis were reported during the last few years, including CdTe particles from elemental Te and cadmium salt precursors,[107] ZnS quantum dots from zinc acetate and thioacetamide in the presence of ionic liquids (IL),[108] vaterite-type, crystalline $CaCO_3$/cellulose composites,[109] as well as $BaTiO_3$ particles from $BaCl_2$ and $TiCl_4$ under basic conditions.[110] Nonetheless, sonochemistry in the water phase was also applied to the preparation of nanomaterials with different morphologies and more complex structures. For instance, PbS nanocrystals prepared from lead acetate and thiourea displayed a spherical, rectangular or cubic morphology depending on the solvent [*i.e.* ethanol, water, EG or PEG] and the source of energy used in the synthesis (*i.e.* US probe reactor or microwave reactor).[111] TEM investigations revealed that the size of nanoparticles obtained in water varied depending on the reactor, with smaller particles (30–50 nm diameter) observed under microwave irradiation, compared to particles obtained by sonication (80–100 nm diameter). When EG was employed as solvent, the difference was even larger (15–35 nm under MW vs 100–150 nm under US), while the opposite trend was observed in the case of EtOH (150–200 nm under MW vs. 10–15 nm under US) and PEG (100–150 nm under

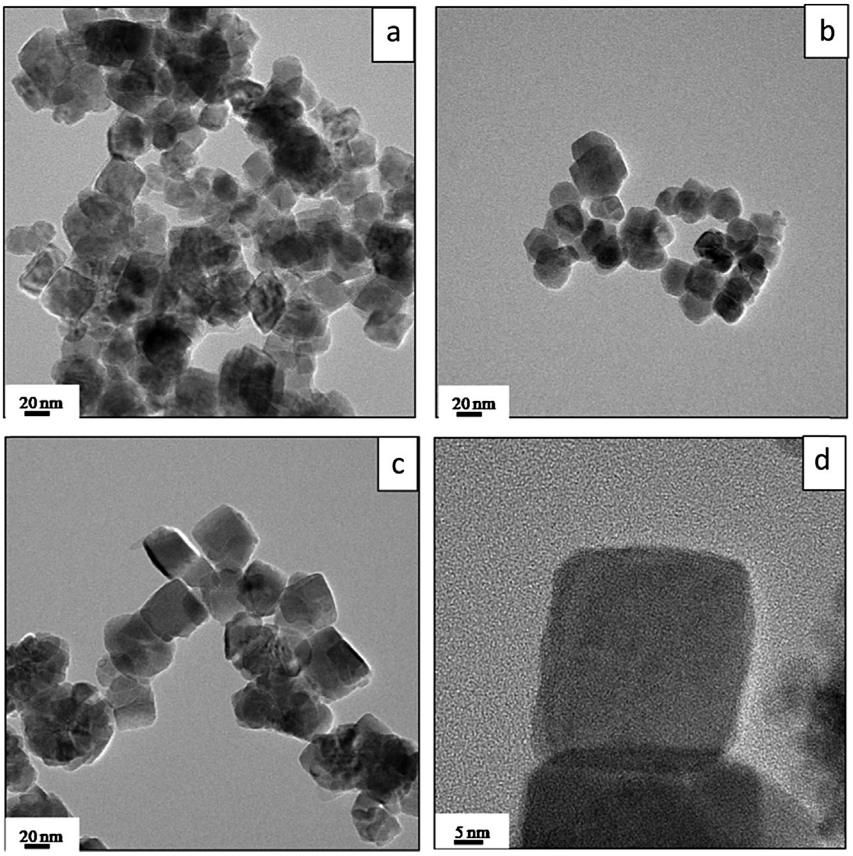


Fig. 9. TEM images of Mn-Zn ferrite nanoparticles synthesized by US method (Image reproduced from reference 97, by kind permission of Elsevier).

MW vs. 20–30 nm under US).

Manganese-based molecular sieves with a cryptomelane-like phase and a three-fold surface area were obtained by Suib and co-workers,[112] using an US-promoted (temperature-controlled cleaning bath) redox reaction between Mn^{2+} and Mn^{7+} precursors at room temperature acidic medium, compared to those prepared by refluxing method. It is worth noting the reaction time could be reduced from 4 h to 2 h by adding 5% acetone as a co-solvent to the aqueous solution. Due to its low boiling point, cavitation was easier to induce in the presence of the organic solvent, which on the other hand, should not be too abundant to evaporate into cavities and to produce a 'cushioning' effect in which vapours resist compression and slow down the implosion of the cavity, reducing the energy transmitted to reactants.

For potential applications as electrode material for super capacitors, MnO_2 nanoparticles were prepared by sonochemical $KMnO_4$ reduction using PEG as a reducing agent in water. A horn type 20 kHz sonicator (100 W/cm^2) with a tip diameter of 13 mm was used, at room temperature for 20 min. The MnO_2 nanoparticles were poorly crystalline in nature, while they were closely spherical in shape, in a size range of 10–20 nm.[113]

A size controlled sonochemical synthesis of highly crystalline super paramagnetic Mn-Zn ferrite nanoparticles in aqueous solution was performed by Abbas.[114] Comparing the US route with the traditional polyol method, the authors demonstrated that in the case of nanomaterials obtained by irradiation, the related shape changed (from sphere to cube) (Fig. 9).

The magnetic properties are modified since the cristallinity is noticeably increased and, as a consequence, such nanoparticles are super paramagnetic at room temperature. Regarding the ultrasonic processor, an apparatus with a maximum power of 1500 W equipped with a titanium horn presenting a 5 cm^2 of irradiating surface area, and with a piezoelectric transducer supplied by a 20 kHz generator, was used.

$NiMoO_4$ nanorods were synthesized by a facile sonochemical procedure employing a probe reactor under mild conditions and non toxic materials, within short reaction times (around 30 min).[115] The authors describe a remarkable influence of the acoustic power on the morphology of nanorods, observing a progressive increase in their length shifting from silent conditions, up to 45 W and, then to 75 W US irradiation (Scheme 23). Other interesting examples of water phase, sonochemical procedures for the synthesis of nanorods, were reported in the recent literature, supporting the increasing interest in US as an alternative energy source in this field of chemistry.[116–118]

As alternatives, inorganic particulates were introduced into sunscreen formulations as alternatives or in addition to organic filters, to better reflect, scatter and/or absorb the electromagnetic radiation. Among these inorganic particulates, inert semiconductor metal oxides like TiO_2 are widely used. However, inert semiconductors are often photoactive producing reactive radical species not properly safe for the skin. Therefore, such particles should be properly treated before their use. In this context, commercial nanosized TiO_2 was coated with lignin to remove the photocatalytic activity of TiO_2, while preserving the UV filter property useful for skin care applications (Fig. 10). The methodology was performed at room temperature and ambient pressure, in water, with vigorous mixing followed by 20 kHz sonication (400 W max power; 0.32 cm probe).[119]

Another composite nanomaterial containing the safely TiO_2 and therefore suitable in biomedical applications (*e.g.* antibacterial) was developed by Jhuang.[120] A shell/core-type geometry silver/titanium oxide nanoparticles were prepared through the sonochemical process, in the presence of EG with alkaline solution. The average particle size was roughly 80 nm, while it was demonstrated that titanium oxide was coated by Ag nanoparticles having a metal grain size of about 2–5 nm, with a 1/3-wt ratio of Ag to TiO_2. The synthetic procedure consisted of an initial preparation of a TiO_2 suspension, in water at room temperature, in presence of EG and sodium hydroxide (3 min of sonication by an ultrasonic probe with 23 kHz and 500 W), followed by the addition of an $AgNO_3$ solution, and with a new sonication for 15 min (same experimental conditions) as detailed in Scheme 24.

Chang and co-workers[121] reported a simple and environmentally friendly synthesis of tungsten trioxide hydrate nanosheets in the range of 10 nm thickness and of 250 nm side length. Sonication was applied by means of a high-intensity US probe (20 kHz, 1000 W), which was necessary to avoid the formation of nonhomogeneous and amorphous particles observed in the corresponding conventional procedure. This was probably due to the

Scheme 23. Schematic representation of $NiMoO_4$ nanorods synthesized under silent conditions (left), US irradiation at 45 W (center), 75 W power (right) (Image reproduced from reference 98, by kind permission of Elsevier).

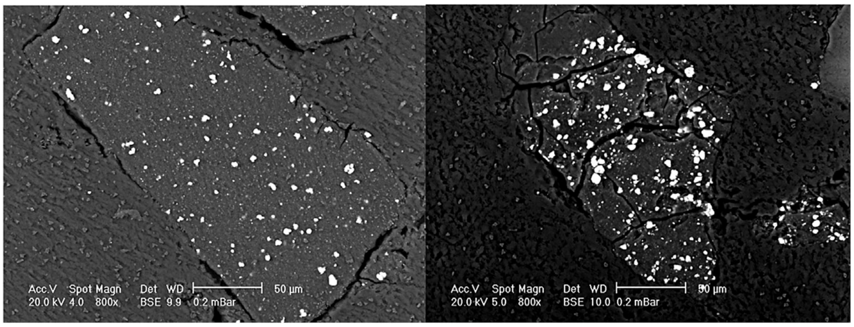


Fig. 10. SEM images of TiO_2/lignin cluster (Image reproduced from reference 102, by kind permission of Royal Society of Chemistry).

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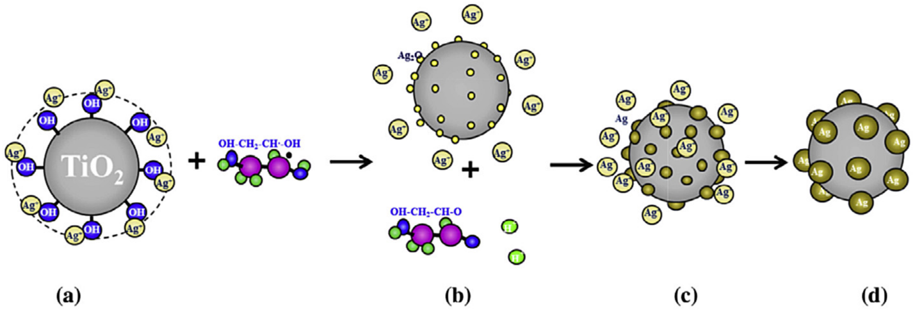


Scheme 24. The mechanism to form Ag/TiO_2 nanoparticles (Image reproduced from reference 103, by kind permission of Elsevier).

enhanced kinetics of $WO_3 \cdot H_2O$ nucleation under US conditions capable of preventing uncontrolled aggregation phenomena.

An efficient method was proposed by Ziarati to prepare CuI nanoparticles via sonication.[68] The size of CuI particles was reduced from 1 μm (typical of particles obtained with traditional methods) to 20 nm (nanoparticles prepared in the presence of ultrasound) with an increase of specific surface area. A US generator equipped with a converter/transducer and a titanium oscillator (12.5 mm in diameter), operating at 20 kHz and 90 W power was used. CuI nanoparticles catalysed efficiently the US-synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones, in water (Scheme 10). A US-assisted Fenton-like reaction between Cu(II) cations and hydrogen peroxide was used to synthesize CuO nanoparticles, in water, at 0–5 °C, under argon atmosphere. Ultrasound, generated by a 20 kHz, 50 W probe, induced the degradation of hydrogen peroxide in •OH radicals and hydroxide anions. The oxygenated species reacted with copper ions to produce directly CuO without the need of sample's aging. These nanoparticles acted as catalysts in the degradation of methylene blue, in the dark, in presence of hydrogen peroxide.[122]

A method to synthesize relatively small diameter silver nanoparticles for biomedical application (*e.g.*, antibacterial properties) without addition of environmentally hazardous reagents was developed by He.[123] Ultrafine silver nanoparticles (average diameter of 8 nm), were obtained through sonication (cleaning bath, 150 W, 50 kHz) of an aqueous alkaline solution by dropwise addition of $AgNO_3$, HO^- playing the role of electron donor. The formation of Ag nanoparticles occurred without any external reducing agent and/or surfactant addition, water acting itself as reducing agent (Scheme 25).

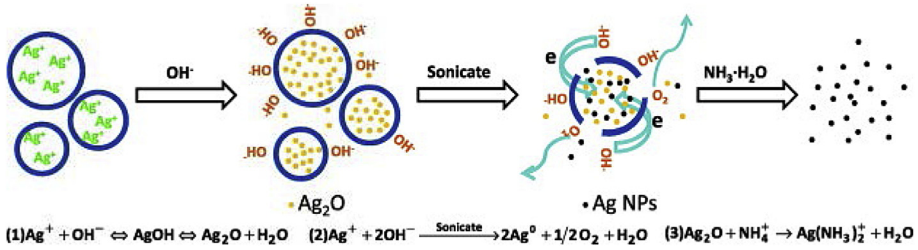
Photoactive micro/nanomaterials were also synthesized through a facial sonochemical route. A preparation of AgSCN micro/nanostructures by using $AgNO_3$ and KSCN was carried out by Salavati-Niasari.[124] Different morphologies of AgSCN were obtained when sonication (30 min) was performed in the presence of a co-solvent, such as ethanol, dimethyl sulfoxide, cyclohexanol, *N*,*N*-dimethylformamide, ethylene glycol or polyethylene glycol. Compared with the sample obtained without sonication, some of the sonicated nanoparticles showed a more intense emission in the visible region (around 550 nm), at room temperature. Experimentally, a multiwave ultrasonic generator, equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz was used for the irradiation. All US experiments were carried out at ultrasonic power between 100 and 110 mW measured by calorimetry.

Sonication of a $Zn(OH)_2$ with a cleaning bath (80 W, 37 kHz) in a basic aqueous solution yielded wurtzite-type crystalline ZnO, which, in the presence of different soluble biopolymers (*i.e.* starch, gelatine, agar or chitosan), formed nanocomposite colloids with promising antifungal properties.[125] Depending on the polymer employed as stabilizer and, hence, on its complexation properties, the authors observed large clusters with a dimension ranging from 200 to 600 nm, containing smaller particles (around 40 nm) with spherical, rice-shaped or egg-shaped morphology (Fig. 11).

Wurtzite-type ZnO could also be obtained by high-intensity sonication (20 kHz, 100 W/cm^2 probe) of an aqueous solution of zinc acetate containing an acidic IL with the double function of preventing aggregation of the growing ZnO nuclei and promoting their growth towards preferential directions.[126] Indeed, different nanoparticle morphologies were observed, depending on the quantity and nature of the added IL, as well as on the time and frequency of the applied US field. Similarly, the sonochemical preparation (33 kHz, 350 W cleaning bath) of ZnO from zinc nitrate in a water/ethanol basic mixture, was enhanced by the addition of ethylenediamine as a chelating agent capable of promoting the crystallization process.[127]

A method to produce high quality ZnO nanoparticles with controllable shape, uniformity, and purity, without any addition of organics, was optimized by Zak.[128] The shape of the nanoparticles can be tuned by varying the US time from 5 to 60 min. Uniform ZnO nanorods, with diameter around 50 nm, were formed after 15 min of sonication, while flower-like ZnO nano-aggregates were formed after 30 min (Fig. 12).

Nanotechnology can provide high durability for fabrics. Green metal oxide nanoparticles are used in textile finishing, altering surface properties and imparting textile function (antibacterial,



Scheme 25. Formation of Ag NPs in alkaline aqueous solution via US irradiation (Image reproduced from reference 106, by kind permission of Elsevier).

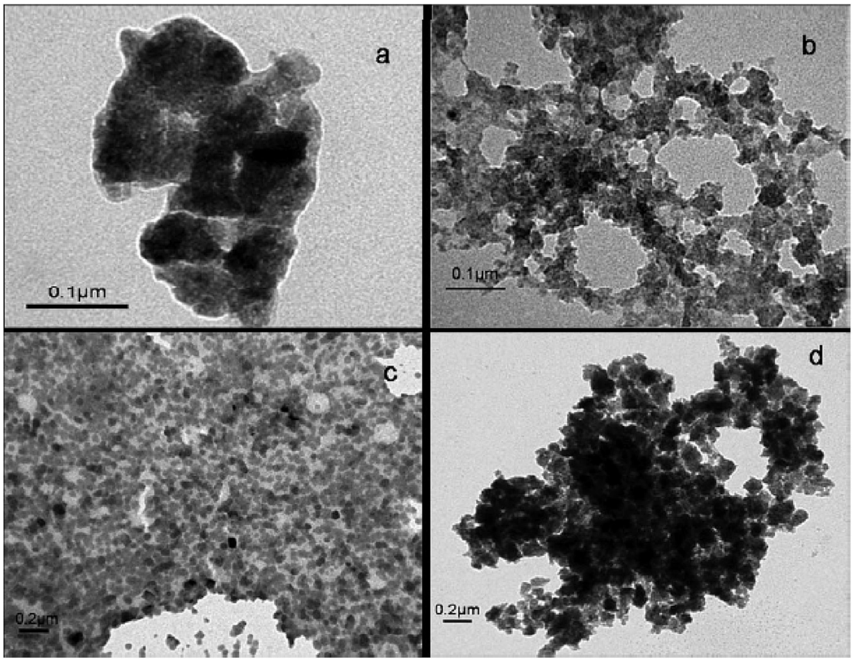


Fig. 11. TEM images of ZnO-biopolymer nanostructures synthesized by sonochemical method with starch (a), gelatine (b), chitosan (c), and agar (d) (Image reproduced from reference 108, by kind permission of Wiley).

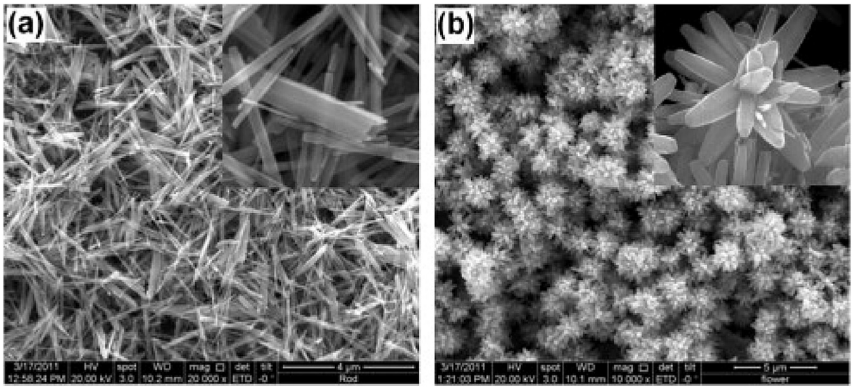
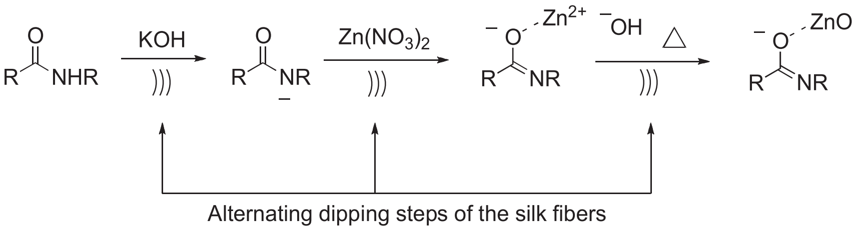


Fig. 12. SEM micrographs for ZnO (a) nanorods and (b) nano-flowers (Image reproduced from reference 111, by kind permission of Elsevier).



Scheme 26. ZnO nanoparticles deposition on silk fabrics.

self-decontaminating, UV blocking functions, etc.). With this purpose, a ZnO nanoparticle's coating was deposited on the surface of silk fabrics by sequential dipping steps, alternating bath of potassium hydroxide and zinc nitrate under ultrasound irradiation (Scheme 26).[129] This kind of covering involves *in situ* generation and deposition of ZnO in only one step. The concentration of reagents, together with the number of sequential dipping steps, were able to influence the growth of ZnO nanoparticles. Furthermore, varying the ultrasound power (305 W vs 138 W) changed the dimensions of nanoparticles.

Selenium nanotubes were synthesized by reduction of H_2SeO_3 with hydrazine hydrate, in water or EG as solvents, performing US irradiation by means of different reactor setups.[130] Interestingly, the quality of the obtained nanostructures varied with the applied US power. Operating a sonication probe at 100 W yielded nanotubes with a high aspect ratio, while increasing the power up to

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300 W led to a progressive loss in tubular structures and to the formation of particles with very low aspect ratio, probably due to the melting of Se structures. Moreover, selenium nanowires were obtained from the synthesized nanotubes by an aging process in solution that induces the collapse of the tubular morphology. A more recent alternative route to selenium nanowires was reported, in which Se nanoparticles, formed *in-situ* by treatment of the metal powder with hydrazine, were sonicated in water, EG or 2-propanol for 1 h.[131] It is worth noting that when methanol, ethanol, acetone or DMF, were used as solvents, nanotubes were obtained instead of nanowires, witnessing once again how the choice of the sonication medium is a crucial issue. As a matter of fact, the authors rationalize the preferential formation of nanowires over nanotubes in water, EG or 2-propanol, on the basis of the generally higher values of surface tension and viscosity of these solvents compared to the other tested liquids.

PVA with a molecular weight (M_W) average of 90000 g/mol was employed as the matrix material for uniformly dispersed, amorphous magnetite nanoparticles (diameters of 10–20 nm), which could be obtained by US irradiation (20 kHz, 100 W/cm^2 probe) of a water solution containing the hydrophilic polymer and iron pentacarbonyl as a precursor.[132] With a similar approach and using the same US setup, the latter polymer was used to stabilize copper oxide nanocrystals, although, in this case, sonication was performed on a less green 10% water/DMF PVA solution.[133]

Even though water is the solvent of choice for the US-promoted nanomaterials synthesis, it is sometimes outperformed by less environmentally friendly reaction media. As an example, Gedanken and co-workers[134] reported the sonochemical preparation (20 kHz, 100 W/cm^2 probe) of metal oxide nanoparticles from aqueous metal acetates, by either oxidation or hydrolysis reactions. In both cases, a 10% water/DMF solution afforded higher yields than pure water as solvent. This result is due to the lower vapour pressure of DMF or water/DMF solutions that minimizes the filling of US-induced cavities with solvent vapours and, hence, increases the amount of energy released during cavitation collapse, compared to water. In a recent study, lead iodide nanoflakes prepared by sonication of Pb foils (20–25 kHz probe reactor) in ethanol as solvent, the presence of iodine, showed a very regular hexagonal morphology. Using a more polar ethanol/water (1/1) mixture, PbI_2 crystals changed from flakes to very large blocks, as a consequence of the accelerated ionization of lead and iodine.[135]

3. Sonochemistry in ionic liquids

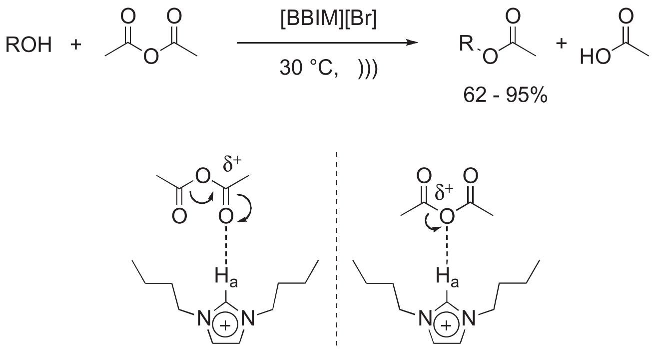
Ionic liquids (ILs) are gaining increasing attention in different fields of research,[136–139] despite the fact their greenness has been questioned. They represent an interesting alternative to conventional solvents for sonochemistry, taking into account the peculiar properties such as the extremely low vapour pressure, the relatively high heat capacity, viscosity and density, which tend to minimize the ‘cushioning’ effect inside cavities and to enhance the absorption of acoustic energy by the reaction mixture. On the other hand, the US-induced micro mixing and mass transfer effects enable the homogenization of reactions in viscous media, like in ILs. Furthermore, simple work-up procedures and the possibility of recycling, increase their appeal as alternative reaction media or additives. Nonetheless, concerns about their use under US irradiation derive from potential cavitation-induced degradation phenomena [(*i.e.* formation of haloalkanes from S_N^2 processes as well as imidazole decomposition by-products (IDPs)[140]]. Release of HF (or BX_3) was observed under harsh conditions from some PF_6^- (and BX_4^-) anion containing ILs.[141,142] Decomposition compounds such as 1,3-butadiene, 1,3-butadyine, 2-methylpropane, acetonitrile/isocyanomethane were also detected by measuring the head-gas composition during sonication of some imidazole-based ILs at 85 °C. In addition, by-products such as *N*-heterocyclic carbenes can be formed by deprotonation at the C-2 position of the imidazolium nucleus,[143] due to the acidity of the H-2 hydrogen ($pK_a = 5$). In the case of hydrophobic bis-(trifluoromethylsulfonyl)imide-based ionic liquids, the proportions of the corresponding degradation products is negligible, but still enough to prevent their recycling.[144] Hence, a reasoned use of these solvents should be applied for prolonged or very high-intensity sonication, taking into account that cavitation might be extremely difficult in an IL, due to large cohesive forces. In the following paragraphs, the synergistic IL/US combination is illustrated for the preparation of heterocycles, polymers, nanosystems as well as for enzymatic reactions, in which the role of IL is not only as a solvent but also as a catalyst or additive in neat conditions. Moreover, depending on the IL used, nanoparticles with different morphologies were obtained and stabilized.

3.1. Ionic liquid-catalysed organic reactions

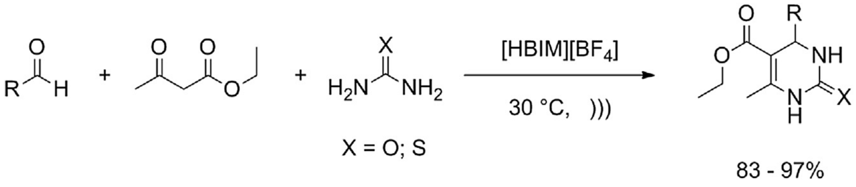
Despite the fact that ILs are normally considered as mere solvents, the interaction between their charged moieties with the functional groups of substrates can efficiently catalyze organic reactions, allowing advantageous, metal-free synthetic conditions. One of the early study in which this effect is combined with US as the energy source was published by Srinivasan and co-workers in 2003.[145] The O-acetylation of a number of benzylic and aliphatic alcohols with acetic anhydride was carried out by means of a 120 W, 50 kHz US cleaning bath, at room temperature. 1,3-di-*n*-butylimidazolium bromide ([BBIM][Br]) was chosen as the reaction medium, hence the catalytic effect is explained by the authors on the basis of the hydrogen bond interaction of the acidic H_a of the imidazolium ion with the oxygen atoms of the anhydride (Scheme 27).

More recently, the same group described the exploitation of similar principles and procedures to the three component synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from aldehydes, ethyl acetoacetate and either urea or thiourea (Scheme 28)[146] in 1-*n*-butylimidazolium tetrafluoroborate ([HBIM][BF_4]) IL, as well as the preparation of 1,8-dioxo-octahydro-xanthene by condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione (Scheme 29).[147]

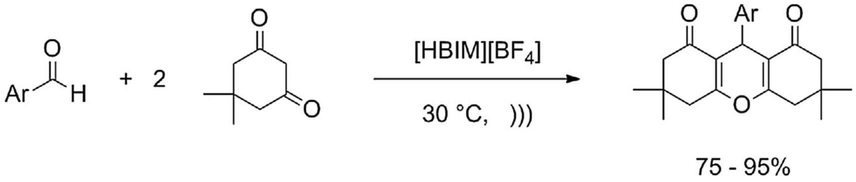
Zhao et al.[148] prepared a Task Specific Ionic Liquid (TSIL) acting as both protic catalyst and solvent in the Knoevenagel reaction, to obtain electrophilic olefins from active methylene and carbonyl derivatives. The ternary adduct prepared by simple mixing of hexamethylenetetramine, CH_3COOH and H_2O (in a 1:1:3 ratio), efficiently promoted the synthesis of α,β-unsaturated esters, starting form aromatic aldehydes and ethyl 2-cyanoacetate. Under ultrasonic irradiation (100 W, 40 kHz), the condensation occurred



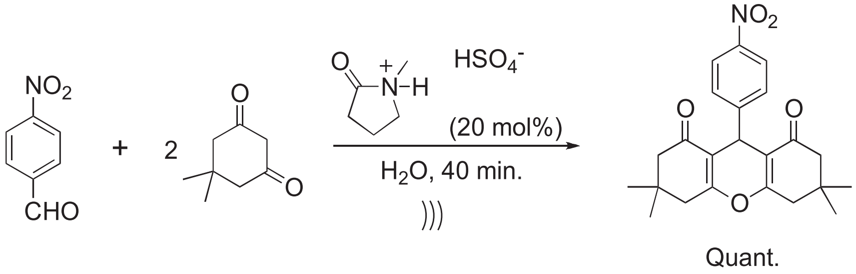
Scheme 27. Acetylation reaction of alcohols.



Scheme 28. IL catalyses Biginelli reaction under US.



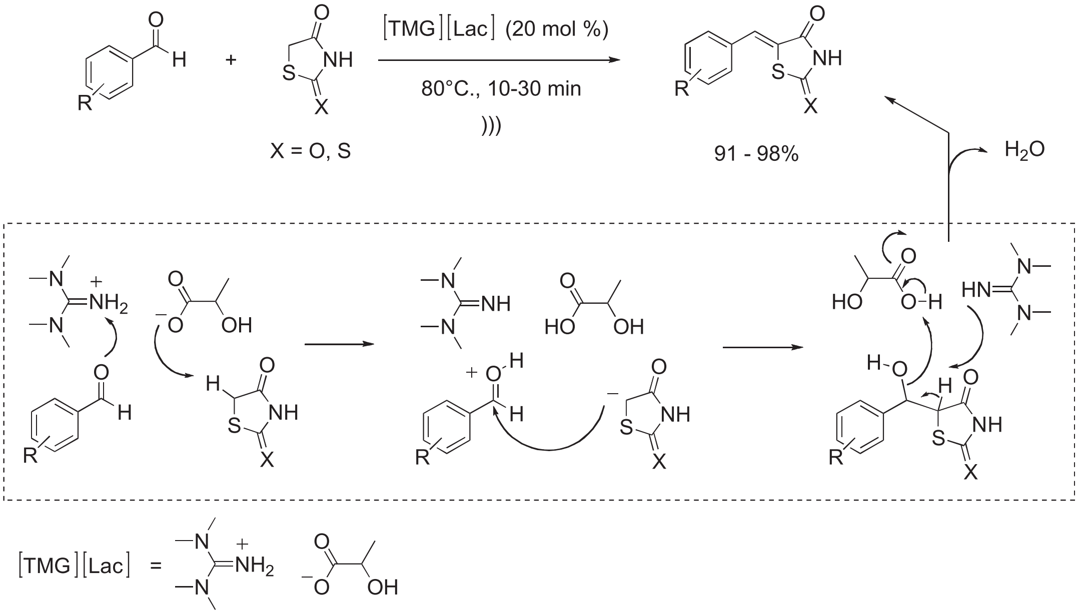
Scheme 29. Aromatic aldehydes condensation.



Scheme 30. Knoevenagel condensation.

with high yields (96%) within 20 min at 40 °C. Moreover, the solvent–catalyst system could be recycled for at least 6 times with no significant loss of activity was observed. The pivotal role of TSILs was also demonstrated in the Knoevenagel reaction leading to 1,8-dioxo-octahydroxanthene derivatives under ultrasound irradiation (with a 6 mm diameter probe operating at 20 kHz) (Scheme 30).[149] The ultrasound-TSIL synergy was beneficial for the condensation reaction of dimedone with various aromatic aldehydes. Faster kinetics and higher yields were obtained, compared to heating using conventional method.

While the use of other biomass derivative solvents, not included in IL family, will be further detailed in Paragraph 4, this section



Scheme 31. Knoevenagel condensation using guanidine-lactic acid based ILs.

reports on the use of biodegradable TSIL such as 1,1,3,3-tetramethylguanidine lactate [TMG][Lac] for the Knoevenagel condensation between 2,4-thiazolidinedione and diverse aromatic aldehydes. The *exo*-double bond was selectively formed, with excellent yields and without formation of any other side product/bis-product or toxic waste (Scheme 31).[150]

The [TMG][Lac] IL acted as catalyst. The lactate anion abstracted the active hydrogen of the 2,4-thiazolidinedione, facilitating its nucleophilic attack on the electrophilic carbon of the carbonyl compound. Subsequent dehydration led to the arylidene products, with water as the only waste, regenerating [TMG][Lac], that could also be recovered and recycled for five runs. Ultrasound promoted faster reactions compared to conventional heating.

Instead, guanidine carbonate as starting material, reacted with aldehydes and cyclic ketones, to access pyridine-2-amine derivatives in [BSO_3HPy][HSO_4] acting both as solvent and catalyst (15 mol%) (Scheme 32).[151] Comparing the results using microwave activation and ultrasound (sonic bath operating at 25 kHz), microwaves led to slightly better yields (90% *vs.* 80%) within shorter reaction times (5 min *vs.* 50 min), in the presence of catalytic quantities of [BSO_3HPy][HSO_4], without any additional solvent. Under US activation, the quantity if TSIL had to be increased to obtain satisfying yields (although still lower compared to MW) and it was used as solvent and recycled four times without significant loss of activity (80%, 78%, 75%, 72%). The TSIL played a pivotal role to expedite formation of the corresponding Knoevenagel adduct in the first step, undergoing Michael addition of guanidine carbonate/cycloaddition/aromatization steps.

US-promoted cycloaddition reactions were carried out by means of a cleaning bath (40 kHz) in [HMI][BF_4] IL (Scheme 33). With few exceptions, similar stereoselectivity values were reported, with a significant improvement of the reaction rates and yields with respect to silent conditions.[152] The role of ILs in the activation of cycloadditions is not obvious. Nonetheless, formation of IL decomposition products with catalytic effects could be ruled out, taking into account the high thermal stability of the employed solvents and the mild reaction temperature (around 30 °C). On the other hand, the authors mention how the US-induced micro mixing and mass transfer effects enable the homogenization of reactions in which the dienophile is not miscible with the rest of the mixture.

2,4-Diarylthiazoles were obtained within short reaction times (<10 min) from arylthioamides and α-bromoacetophenones, at room temperature, using [BMIM][BF_4] as both solvent and catalyst (Scheme 34), using a sonication probe operating at 140 W and 24 kHz.[153] Lower US intensity values, as well as organic solvents were tentatively screened. For the model synthesis of 2-phenyl-4-(4-bromophenyl)thiazole, a marked drop in the system activity was observed, while [BMIM]-based ILs with different anions yielded, in the same experimental conditions, only slightly worse results. Work-up consisted of a simple quench and extraction step and the products obtained after evaporation to dryness did not need further purification, highlighting the efficiency of this procedure.

Electrochemical reactions in ILs are affected by the problem of high viscosity and consequently low diffusion coefficients. Hence, ultrasounds were used to enhance mass transfer and promote the electro reduction of *N*-methylphtalimide into 3-hydroxy-2-methylisoindolin-1-one at room temperature, in 1-ethyl-3-methylimidazolium bis-(trifluoromethanesulfonyl)imide ([C_2MIM][NTf_2]) as solvent (Scheme 35).[154] Sonication improved conversion values and charge efficiency, leaving selectivity unaffected. On the other hand, when temperature was raised to 60 °C and sonication time prolonged to 14 h (US probe with 95 W/cm^2 intensity), darkening of the IL was observed and bis(trifluoromethanesulfonyl)imide decomposition (*c.a.* 1 mol %) produced the release of 423 ppm of fluoride.

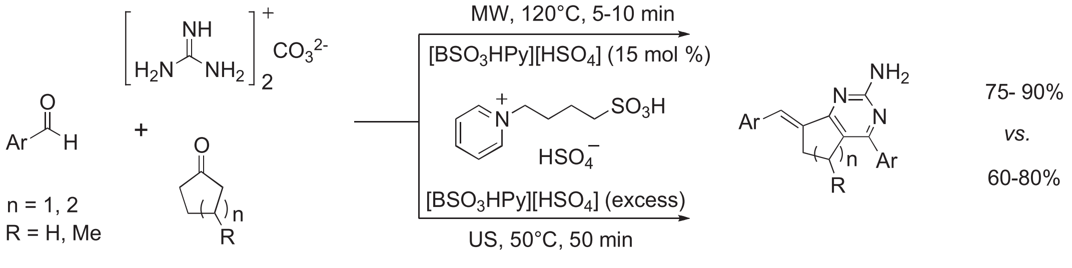
The tandem addition/annulation reaction of *o*-aminoaryl ketones with α-methylene ketones yielded quinoline derivatives in short sonication times (*i.e.* 35 min) at ambient conditions, employing a thermostated cleaning bath (Scheme 36).[155] Due to the high basicity of its anion compared to ClO_4^-, Br^- or Cl^-, the IL 1-butylimidazolium tetrafluoroborate ([HBIM][BF_4]) afforded the best results. Nonetheless, optimal conditions were attained by the addition of methanol (25 vol %) as a co-solvent, which increased the substrate solubility. A control reaction under silent conditions gave a very low yield (<5% *vs.* 74% with US) and the system could be re-used twice without loss of activity.

An analogous beneficial co-solvent effect was demonstrated for the sonochemical Erlenmeyer synthesis of azlactones in a 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6])/MeOH (2:1 v/v) mixture, using a 40 kHz Cleaning bath (Scheme 37).[156]

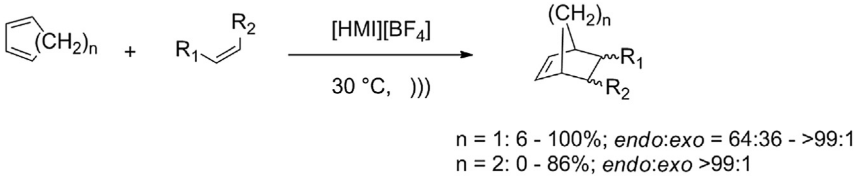
The preparation of 4-arylidene-2-phenyl-5(4)-oxazolone (azlactones) derivatives was also investigated using dicationic ionic liquid-polyoxometalate (POM) catalyst such as [$C_6(MIm)_2$]$_2$[$W_{10}O_{32}$], incorporating 1,6-bis(3-methylimidazolium-1-yl)hexane as cation and $W_{10}O_{32}$ as anion (Scheme 37).[157] At room temperature, either in the absence of catalyst or performing the reaction in silent conditions, led to low yields (5%). Upon heating (at 80 °C) without ultrasound, the yield was increased (60%), but was still moderate compared to the reaction performed under ultrasound activation.

Similarly, the benefits of combining ultrasound irradiation and ILs were confirmed for the preparation of highly substituted pyrimidine derivatives. In this case, *n*-dibutyl ammonium chlorosulfonate [n-Bu_2NH_2][$ClSO_3$], acting as both solvent and catalyst, was used to perform the multi-component reaction involving aminobenzimidazole, aldehydes and β-ketoesters (Scheme 38).[158] Conventional heating at high temperatures (60–100 °C), with or without polar or apolar organic co-solvents, led to moderate yields after 10 h. The reaction kinetics was highly accelerated when using ultrasound activation, avoiding any extra solvent, and leading to clean syntheses with consequent easy recycling of the solvent for five successive runs (95, 93, 90, 89 and 87% yield respectively).

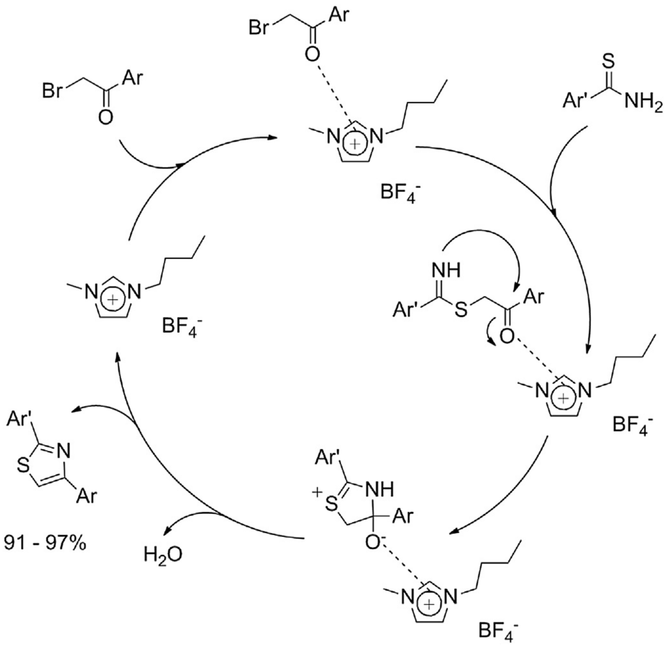
Concentrated (neat) medium resulted more efficient, probably because the solid catalyst facilitated the active hosting sites for the



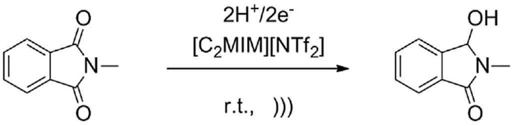
Scheme 32. Cascade domino reaction to polycyclic pyridine-2-amines.



Scheme 33. Mass transfer enhanced by US-promoted cycloaddition reaction.



Scheme 34. Fast preparation of thiazoles in [BMIM][BF$_4$].



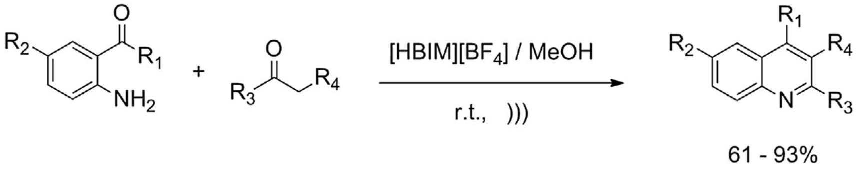
Scheme 35. Improved conversion for the redox system.

substrates, accelerating the reaction rate of the Knoevenagel condensation between the enolic form of the active methylene compound and the aldehyde. The Michael addition, followed by intramolecular concerted cyclization, led to polycyclic pyrimidines (Scheme 38).

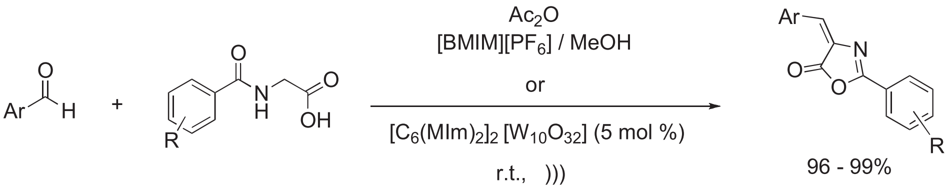
In some sonochemical reactions, ILs are used in catalytic or stoichiometric amounts rather than in large excess. For instance, aldehydes and acetic anhydride reacted to form 1,1-diacetates in good yields, in neat sonochemical conditions (50 kHz thermostated cleaning bath) using a low quantity (*i.e.* 10 mol%) of 1-butyl-3-methylpyridinium hydrogen sulphate ([BMPy][HSO$_4$]), employed as Brønsted acid (Scheme 39).[159]

When conventional solvents were tentatively added to the reaction mixture, both lower yields and reaction rates were observed. The same negative effects were observed when replacing US with mechanical stirring, demonstrating how both the use of ILs as solvent and US as the energy source, contributed to the efficiency of 1,1-diacetates formation. The authors demonstrated the reusability of the IL for three cycles, with only a modest decrease in the reaction yield (97%, 95% and 90% respectively). As a further example, the Fischer esterification of lactic acid was efficiently performed in mild conditions, in the presence of 20 mol% of SO$_3$H-functionalized TSILs (Scheme 40), with no additional solvent under low-intensity US irradiation (40 kHz, 250 W thermostated cleaning bath).[160] Satisfactory conversions and yields were obtained within 4–6 h and the ILs could be easily recovered and recycled five times without observing any decrease in its catalytic activity.

C–C Bond formation through an intramolecular cyclization has become one of the most efficient method for the synthesis of carbocyclic and heterocyclic compounds. The synthesis of 4(3*H*)-quinazolinones by condensation of anthranilic acid, carboxylic acids and anilines, was carried out in the presence of 1 equivalent of [BMIM][BF$_4$] (Scheme 41).[161] Excellent yields were obtained under solvent-free conditions within short times of reaction (7–20 min),



Scheme 36. Tandem addition/annulation reaction.



Scheme 37. Preparation of azlactones by Erlenmeyer-Plöchl.

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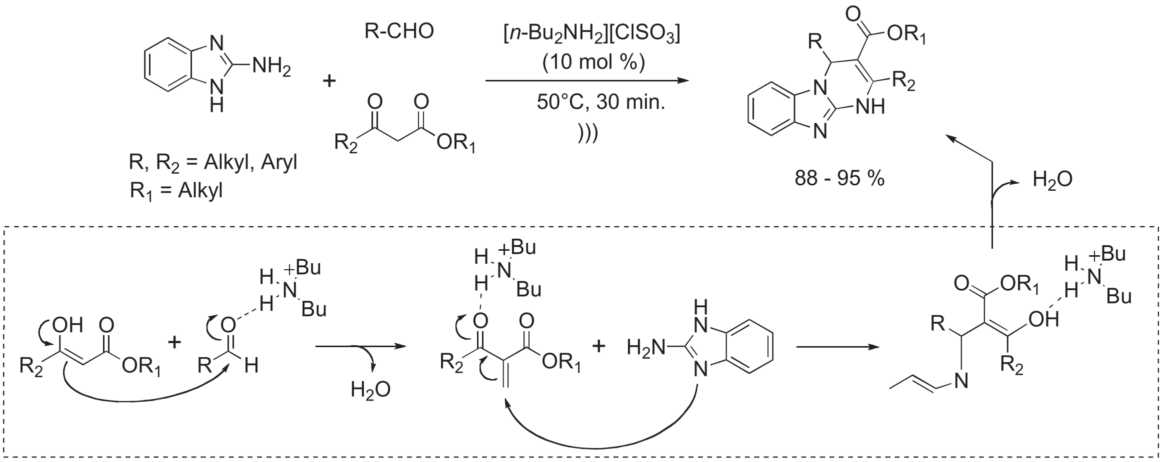
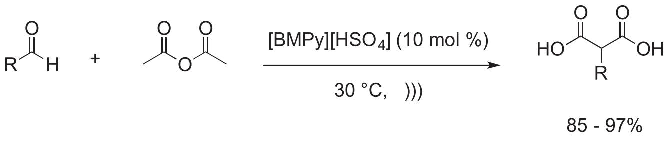
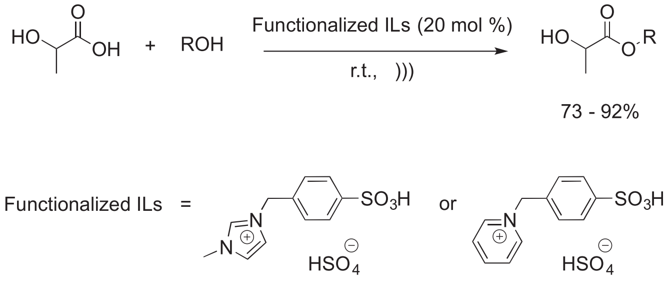


Scheme 38. Mechanism of action of a task-specific ionic liquid for multi-component reaction.



Scheme 39. Preparation of diacetates.



Scheme 40. TSILs for esterification reaction.

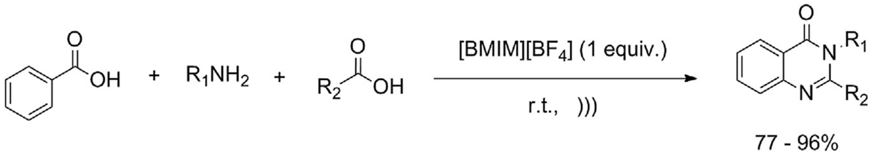
at room temperature, employing a 25 kHz, 500 W ultrasonic cleaning bath. When the reactions were tentatively repeated under conventional magnetic stirring (30 min), no expected product was detected.

[BMIM][BF_4] was also both an efficient catalyst and solvent for the preparation of 2,3-disubstituted benzo[*b*]furans.[162] Upon sonication, the reaction was faster (30 min), and higher yields were obtained compared to thermal activation by microwaves or classical heating.

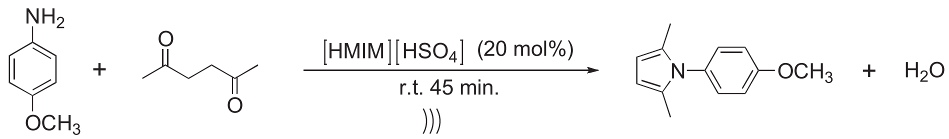
Further contributions include the reaction of nitroalkanes with α,β-unsaturated carbonyl compounds to obtain γ-nitroketones or γ-nitroesters,[163] as well as the preparation of 3,4-dihydropyrimidine(1*H*)-(thio)-ones through the one-pot three-components Biginelli reaction,[164] and the Paal-Knorr reaction to prepare functionalized pyrroles (Scheme 42).[165] The reaction was improved by the use of ultrasound and, among the potential catalysts, 1-methylimidazolium hydrogen sulphate [HMIM][HSO_4] IL represented a solution that avoided the use of toxic metals. The reaction between 2,5-hexanedione and substituted aromatic primary amines, under ultrasonic irradiation (45 min, using an ultrasonic reactor with a frequency of 40 kHz and a nominal power of 250 W), led straightforwardly to N-substituted pyrroles (Scheme 42).

The efficiency of several basic-functionalized IL as catalysts was demonstrated by Paixão,[166] in the Michael addition between substituted β-nitroalkenes and five different 1,3-dicarbonyl compounds, under neat experimental conditions and continuous ultrasonication (Scheme 43). The desired conjugate adducts were obtained in high yields (60–99%), within short reaction time (30 min) and low loading of catalyst (30% mol). Worthy of interest is also the fact that the catalyst could be recovered and re-used at least for four times, without any significant decrease of its activity.

Substituted 2-hydroxychalcones were prepared by the Claisen–Schmidt condensation. Substituted 2-hydroxy-acetophenone



Scheme 41. Three-components preparation of quinazolinones.



Scheme 42. Paal-Knorr synthesis of substituted pyrroles.

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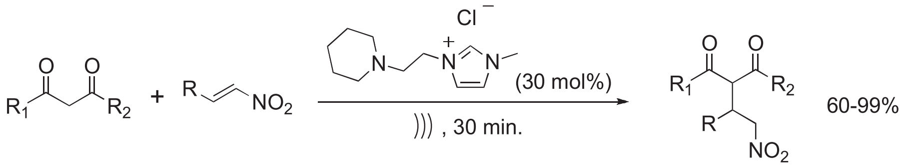
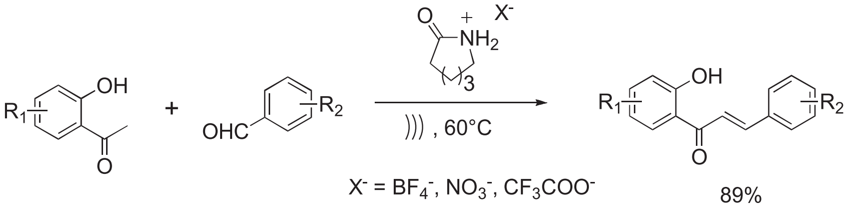


Scheme 43. Michael addition.



Scheme 44. Claisen-Schmidt condensation.

reacted with benzaldehydes in the presence of ILs and under ultrasound irradiation (US cleaner with a rated input power of 120 W) (Scheme 44).[167] 2-Hydroxychalcones were selectively obtained in around 89% yield and were easily separated, due to their very low solubility in ILs, facilitating also recycling ILs.

1,4-Dihydropyridines are important compounds as mimic for the *in vitro* NADH reduction process. Their one pot, three-component synthesis of Hantzsch, was realized by using the 3,3-thionyl-bis-1,10-methylimidazolium chloroaluminate IL as catalyst, in good to excellent yields. Although such reaction occurred without any catalyst and in the absence of sonication, in the presence of 5 mol% of catalyst with sonication, at room temperature, led to yields noticeably increased (close to 100%) in shorter reaction times (30–60 min instead of 180 min).[168]

Another interesting synthetic approach leading to 1,4-dihydropyridines was described by He et al.[169] 4-Substituted-1,4-dihydropyridine-3,5-dicarboxylates were prepared in neat conditions, by direct sonication (with a 3 mm wide and 140 mm long probe) at 60 °C, using a Brønsted acid functionalized imidazolium IL salt (1-carboxymethyl-3-methylimidazolium tetrafluoroborate) (5–15 mol %) as catalyst. The operating frequency was 24 kHz, while the optimum output power was set at 300 W through manual adjustment. Compared to the conventional thermal methods, ultrasound-assisted reactions were shorter (2–10 min) and high yielding (76–95%). Furthermore, the catalytic system could be recycled without significant loss of activity.

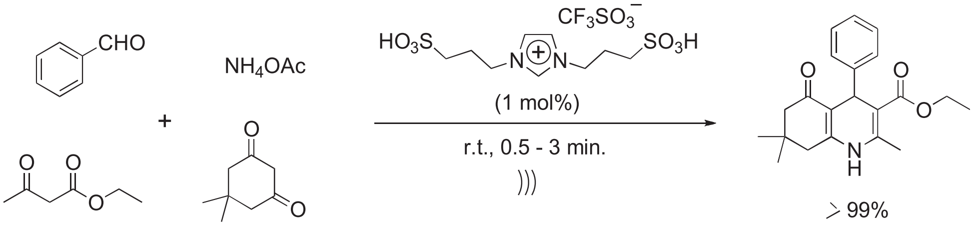
To improve the catalytic activity in the Hantzsch reaction, a TSIL bearing two alkylsulfonic moieties on the imidazolium cation was used as catalyst, to prepare polyhydroquinolines via four-component condensation reactions of aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate (Scheme 45).[170] The reaction mixture, containing 1 mol % of catalyst, was irradiated at room temperature in neat conditions under 35 kHz of frequency sonication, leading to an almost quantitative yield of polyhydroquinolines in a short reaction time. The catalyst was recycled ten times without any sensitive decrease in activity (yields of expected products from 97% to 85%).

Other papers, out of the scope of this review, describe the use of low amounts of ILs as catalysts in US-enhanced reactions with conventional organic solvents employed as main components of the reaction mixture.[171,172]

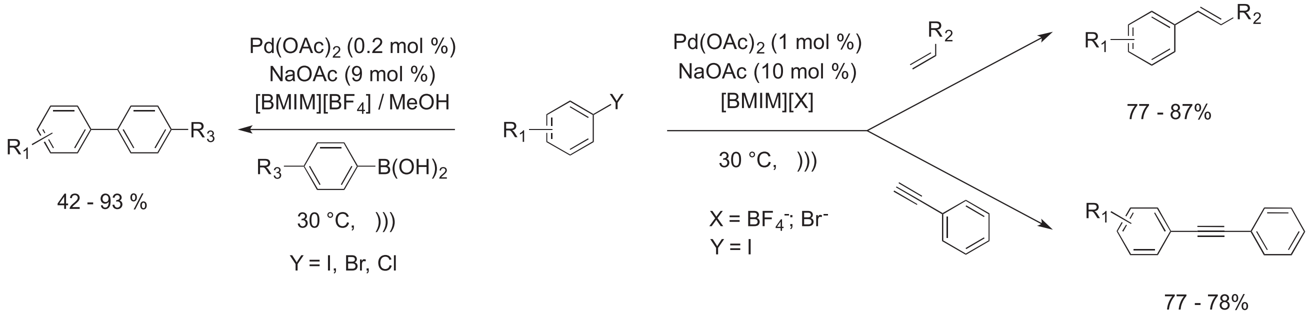
3.2. Organic reactions requiring external catalysts

Although not frequently reported, certain US-promoted organic transformations require the addition of an external catalyst (metals or enzymes) even when performed in ILs as solvents. Pd-catalysed C–C coupling is one of the most investigated class of reactions in this area. An early work by Srinivasan[173] described an elegant US-enhanced procedure (50 kHz cleaning bath) for the synthesis of substituted olefines and alkynes by fast, Heck coupling at room temperature (Scheme 46).

1,3-Di-*n*-butylimidazolium bromide ([BBIM][Br]) and 1,3-di-*n*-butylimidazolium tetrafluoroborate ([BBIM][BF_4]) ILs, were used as solvents, in the presence of $Pd(OAc)_2$ or $PdCl_2$ precursors. They facilitated the *in situ* formation of a Pd(II)-bis-carbene complex (Fig. 13) that was converted during the olefin formation into an IL-stabilized Pd(0) clusters. The whole process was promoted by sonication. Indeed, no reaction took place under silent conditions. Similarly, no conversion could be observed when replacing ILs with conventional solvents such as DMF or NMP, even with the addition of a phosphine ligand. Shortly afterwards, the same group applied the aforementioned conditions to the Suzuki cross-coupling of halobenzenes with phenylboronic acids, in the presence of methanol as a co-solvent to optimize the reaction medium homogeneity (Scheme 46).[174]



Scheme 45. Hantzsch synthesis of 1,4-dihydropyridines.



Scheme 46. Pd-catalysed cross-coupling reactions.

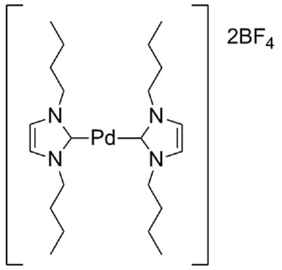


Fig. 13. Pd(II)-biscarbene complex formed *in situ* during Heck and Suzuki coupling reactions.

The Sonogashira coupling reaction was also reported using biodegradable 3-butoxycarbonyl-1-methylpyridinium bis(trifluoromethanesulfonyl)imides ILs, derived from nicotinic acid as solvents, emphasizing the absence of any added cocatalyst or phosphine-based ligand for the Pd-based catalyst.[175] Various substituted aryl iodides reacted with phenylacetylene yielding the corresponding alkynes in good to excellent yields (Scheme 47).

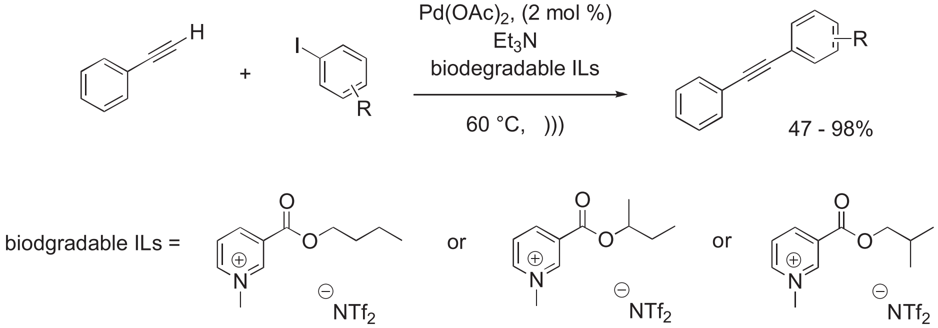
Among other classes of reactions, a Mn-metalloporphyrin catalysed epoxidation of alkenes under US irradiation (microtip probe reactor) was performed in the pyrrole-based IL [MOPYRRO][NTf$_2$] (Scheme 48). A particular reaction mechanism was promoted by sonication.[176] Epoxidation via the bicarbonate-activated hydrogen peroxide (BAP) system was hampered in favor of a classical high-valent oxo manganese porphyrin intermediate. Indeed, the BAP system relied on the formation of the active peroxymonocarbonate ion HCO_4^- from H_2O_2 and HCO_3^- and the US-induced cavitation favoured the dissociation of H_2O_2, hence reducing the concentration of species available for the reaction. Furthermore, the authors pointed out that the use of an IL solvent allowed an optimal solubilization of the porphyrin catalyst, as well as of hydrophilic or hydrophobic substrates.

A one-pot oxidation of alcohols was reported by Matuszek et al.,[177] and applied to the ε-caprolactone production, a monomer extremely important for the synthesis of nylon-like polymers. Potassium peroxymonosulfate was used as oxidant, the 2,2,6,6-tetramethylpiperidine-1-oxyl/tetrabutylammonium bromide as catalyst, in solvents such as 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF$_4$] and 1-butyl-3-methylimidazolium dicyanamide [BMIM][NCN$_2$] (Scheme 49). The oxidation of cyclohexanol afforded 81% of the corresponding lactone within 5 h by indirect sonication (ultrasound bath at 40 °C). The same reaction, carried out in a microwave reactor led to the same lactone in a comparable yield but in a shorter reaction time (30 min).

The combination of [BMIM][BF$_4$], ZrOCl$_2$/NaNH$_2$ and ultrasounds allowed the preparation of thioarylpyridines via a three-component anionic domino reaction involving Knoevenagel condensation/Michael and thiolate addition/cyclization-aromatization-oxidation sequence (Scheme 50).[178] No reaction took place in the absence of one of these elements, even under ultrasound, indicating that only their synergy was effective. The ionic liquid, containing the catalytic system, could be re-used with a faint gradual decrease in the activity (92%, 92%, 91%, 90%, 88% yield over five reaction cycles).

In biocatalytic reactions, a lower enzyme activity is normally reported in IL solvents, compared to common organic solvents. However, US were successfully tested as an alternative energy source with the aim of counterbalancing this negative effect. As an example of US-enhanced enzyme-catalysed reactions in ILs, the glucose transesterification with vinyl laurate by the lipase ‘Novozym 435’ was performed in [BMIM][TfO] at 40 °C by means of a thermostated US cleaning bath.

As more attracting industrial alternative, the glucose direct esterification with lauric acid was carried out in the same experimental conditions, but raising the temperature to 50 °C and adding a molecular sieve to remove water (Scheme 51).[179] Novozym 435 was also used for caffeic acid methylation in 1-butyl-3-



Scheme 47. Sonogashira reaction in biodegradable ILs.

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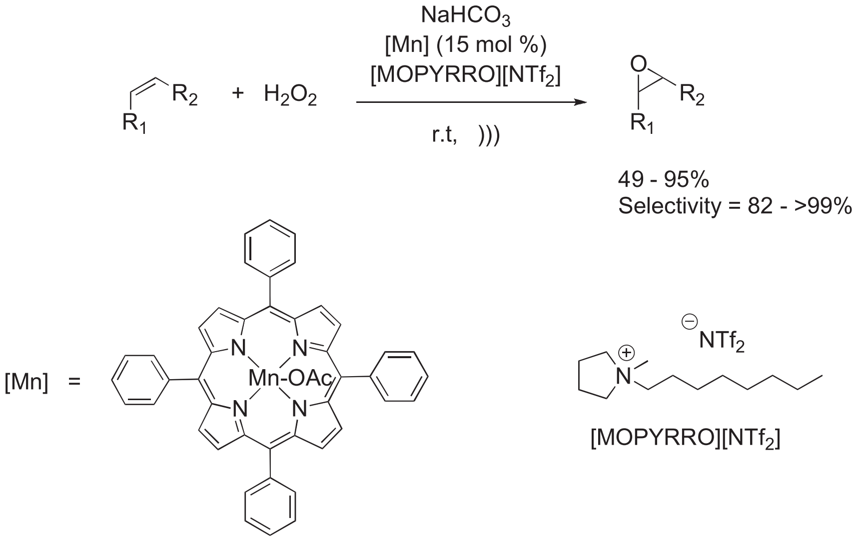
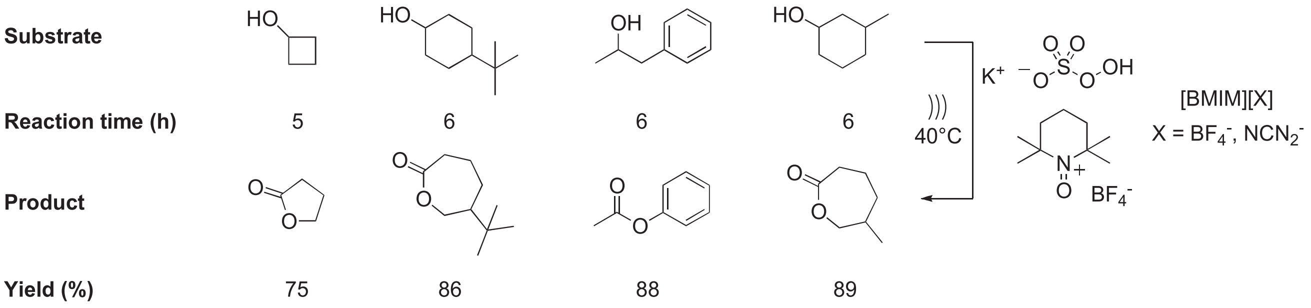
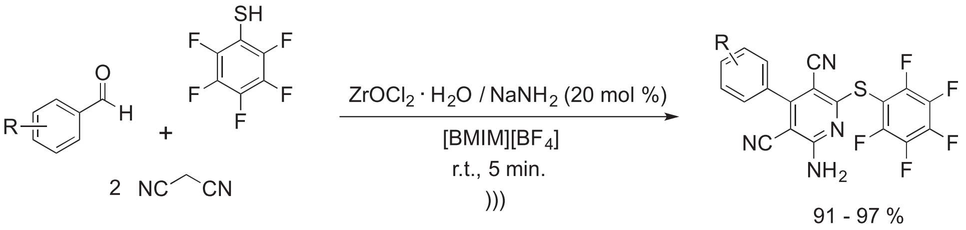


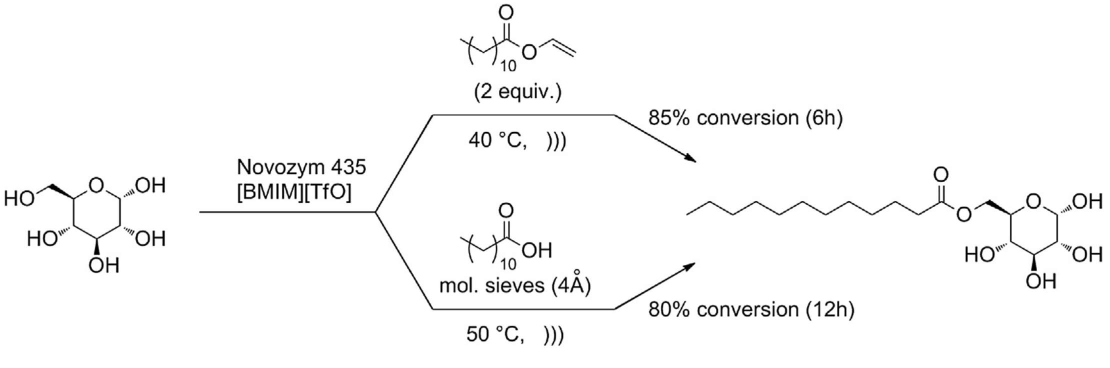
Scheme 48. Mn-catalysed epoxidation of alkenes.



Scheme 49. Oxidation of alcohols.



Scheme 50. Zr-catalysed cascade three-component reaction to thio-arylpyridines.



Scheme 51. Enzymatic glucose transesterification.

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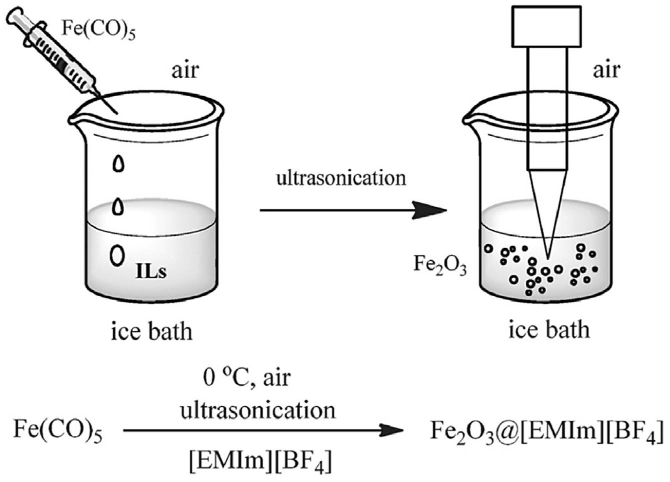
methylimidazolium bis(trifluoromethylsulfonyl) imide) [BMIM][NTf_2] under ultrasound irradiation.[180] Methyl caffeate was proved to be a α-glucosidase inhibitor, scarcely available since it is obtained almost exclusively by chemical synthesis. A quantitative yield is obtained using a pulsed US irradiation frequency (at 25 kHz and with a power of 150 W), after 9 h at 75 °C.

Most of the examples described so far showed the use of ILs as solvents and/or catalysts in ultrasound promoted reactions. However, some examples are known in which ultrasounds are used for the preparation of ILs. This class of reaction will be further detailed in paragraph 5. A question still needing to be answered concerns the possible relationship between the efficiency of the ultrasound-assisted reaction as a function of the structure of the IL used to perform a specific transformation. Data available in the literature are not enough exhaustive to answer without ambiguity to this question, but this fact can not be excluded. It has been shown that similar results were obtained when the structure of the IL was modified by changing the nature of the anion (Schemes 44 and 46) or the cation (Schemes 40 and 47) only. The intrinsic properties of IL solvent can be 'finely tuned' by the careful association of both the anion and the cation, also affecting the shear viscosity of the medium. Taking into account that the outcome of ultrasound −promoted reactions also depends on the viscosity of the system (and not only), any modification of the IL structure will affect the viscosity of the system. Indeed, the absorption coefficient α, describing the way in which the waves are propagating into the medium, will be modified, with a direct impact on cavitation itself.

3.3. *Synthesis of nanoparticles and nanostructures*

A thiol functionalized IL was used both as solvent and stabilizer in the sonochemical preparation of uniformly dispersed, small sized gold nanoparticles.[181] H_2O_2 was used as the reducing agent for $HAuCl_3$, instead of $NaBH_4$, which simplified the addition and purification steps. Based on the poor results of the reaction control under conventional stirring, the authors suggested that US irradiation (40 kHz, 80 W bath) was required for the formation of H• and OH• radicals involved in the reduction mechanism, as well as for the optimal dispersion of the IL-stabilized nanoparticles.

In view of their use as components for liquid magnetic marbles, Deng and co-workers described the preparation of Fe_2O_3 nanoparticles by sonochemical decomposition of an iron pentacarbonyl precursor, in 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM][BF_4]) solvent, under air atmosphere, at 0 °C (Scheme 52).[182] US were applied to the mixture for 90 min by means of a probe reactor operating at a 0.1 W very low power. Both aggregation and sedimentation of particles were prevented by the ILs, and no additional stabilizer or capping agent was required.



Scheme 52. Synthesis of iron oxide nanoparticles in [EMIM][BF_4] (Image reproduced from reference 163, by kind permission of Royal Society of Chemistry).

Zinc oxide nanoparticles were obtained by mixing a water solution of $Zn(OH)_4^-$ ions (obtained from zinc acetate with NaOH) and 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide ([HMIM][NTf_2]), that was then sonicating the mixture (40 kHz, 50 W probe) for 1 h.[183] In the absence of US as well as of the IL, the white ZnO precipitate was not formed. The role of $[HMIM]^+$ cations in the polarization of $Zn(OH)_4^-$ anions by electrostatic attraction was pointed out to explain the increased tendency towards dehydration and oxide formation. However, several examples of sonochemical synthesis of ZnO-based nanoparticles and nanostructures in ILs were recently reported. ZnO nanostructures of different shape and size, depending from irradiation time and IL used, were synthesized and tested as photocatalysts in the photodegradation of methyl orange. The photoactivity was observed to be as high as 95% for ZnO nanoparticles obtained with 1-decyl-3-methylimidazolium bis(-trifluoromethylsulfonyl) imide. ZnO nanosheets were formed when irradiation (45 kHz, 60 W) was performed for short times, while after longer irradiation time, nanorods were obtained.[184] ZnO nano-aggregates, with morphologies depending on the presence or not of a IL, were obtained by Rabieh.[185] Spherical nanoparticles were obtained when 1-butyl-3-methylimidazolium chloride [BMIM][Cl] was used, from disk-like nanoparticles observed in the control reaction without IL. Sabbaghan[186] described the formation of uniform 2D ZnO nanostructures by the ionic liquid-assisted sonochemical method. They obtained nano-aggregates like nanoleaves and nanosheets, working at 40 kHz and 70 W for 30 min under ambient conditions, depending from the IL used. Finally ZnO nanoparticles doped with lanthanide elements such as Ln(III), Eu(III) and Nd(III), were studied by Gao et al.[187] who used 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] in an ultrasound bath operating at 20 kHz and 150 W for 3 min.

By associating ultrasounds and ILs, nanostructured TiO_2 nanoparticles were also obtained. Anatase nanoparticles were obtained when titanium tetraisopropoxide was used as a precursor. The reaction was carried out in an ultrasound bath (45 kHz and 60 W) for 9 h at room temperature. The morphology of nano-anatase was controlled by the nature of cation in the IL. For the majority of ILs that were used, nanospheres were formed, with some exceptions leading to nanorods and spindle-shaped particles. In some preparative experiments, an anatase sample containing small amounts of brookite was obtained. The photocatalytic activity of such material was comparable with that of the commercial P25 TiO_2.[188]

Micro and nano nickel sulphide is particularly important for applications in catalysis, magnetic devices, rechargeable batteries etc. A novel synthetic methodology was reported for the preparation of NiS submicron particles, in 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4] using sonochemical technique.[189] The reaction mixture, obtained by addition of the precursor to a combined solvent mixture (ethanol and IL in a 8:2 ratio), was then exposed to 20 kHz and 100 W irradiation through a Ti horn of 0.635 cm diameter.

Quantum dots made by ZnS have been prepared by a sonochemical route using a ternary solvent composed of acetone, ethyl acetate and *N*-decylpyridinium tetrafluoroborate. ZnS nanoparticles were also formed in the absence of sonication and in water, rather than in the mixture of organic solvent. The authors obtained particles of about 8 nm, when the metal salt concentration was fixed, simply by substituting the water with the IL/organic solvent mixture. Finally, association of ultrasounds and IL allowed to further reduce the diameter of nanoparticles to 2−3 nm. The

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ultrasonic treatment of sols was performed in a Cleaning bath for 5 min (25 kHz and 150 W).[190] The preparation of carbon-based nanostructures (namely nanotubes and their nanoparticles-containing hybrids) was also enhanced by the combination of IL-nanostructure supramolecular interactions and US irradiation in the so-called ‘ionic liquid-assisted sonochemical (ILAS)-method’ described by Park and co-workers.[191,192]

The previous examples clearly show that the nature of the IL has a direct influence on both nanoparticle shape and size, and acts as a stabilizer to prevent their aggregation.

3.4. *Coordination chemistry involving ionic liquids*

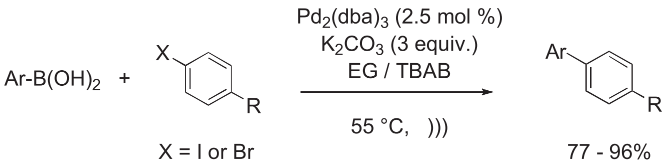
Inorganic synthesis in ILs was rarely carried out under US irradiation. Together with the palladium catalyst formed *in situ* (Fig. 13), two interesting studies by Gedanken and co-workers described the preparation of Fe(II)- and Ni(II)-imidazole complexes neutralized by the anion originated from the IL used as the reaction solvent.[193,194] Fe(1-methylimidazole)$_6$(BF$_4$)$_2$ and Ni(1-methylimidazole)$_6$(BF$_4$)$_2$ were obtained by US-induced (20 kHz, 40 W/cm^2 probe) decomposition of the carbonyl precursors Fe(CO)$_5$ and Ni(CO)$_4$, in the presence of 1-methylimidazole and [BMIM][BF$_4$] as solvent. Fe(1-methylimidazole)$_6$(PF$_6$)$_2$ and Ni(1-methylimidazole)$_6$(PF$_6$)$_2$ were obtained, in the same experimental conditions, when [BMIM][PF$_6$] was used. No metal oxides were formed as by-products and no PF_6^- hydrolysis took place during sonication. Moreover, while only crystalline complexes were successfully synthesized in ILs, amorphous products were obtained when the same reaction was carried out in organic, non-volatile solvents.

4. Sonochemistry in ethylene glycol, PEG, glycerol and other biomass-based green solvents

4.1. *Reactions in ethylene glycol and its oligomers*

Some examples of sonochemical reactions in green solvents such as EG and its oligomers (DEG, TEG and low molecular weight liquid PEG) have already been mentioned earlier in this review,[73,97,102,109,111,116] referring to papers in which their use is combined with, or compared to, the use of water. Liquid or solid PEGs have been effectively employed in catalysis as phase-transfer agents,[195] metal nanoparticles stabilisers,[196] and as safe solvents with high boiling points.[197] This family of solvents is rather frequently employed in combination with microwaves, but less common it is their use in US-activated process. Nonetheless, some remarkable cases can be found in the literature, and they are illustrated below.

A phosphine-free Suzuki cross-coupling was successfully performed in EG, in the presence of 2.5 mol% Pd$_2$(dba)$_3$, tetrabutylammonium bromide (TBAB), and potassium carbonate as an auxiliary base employing a 47 kHz, 250 W cleaning bath (Scheme 53).[198] High yields of biaryl compounds were obtained in pure EG, while water and an EG/water (20 vol%) mixture were tested as alternatives, yielding less satisfactory results. On the other hand, recycling of the system showed a significant and progressive decrease of activity, already in the second run.



Scheme 53. Suzuki-Miyaura cross-coupling.

A PEG-400-InCl$_3$ catalytic system was explored for the one-pot two steps preparation of spiroquinoline derivatives from arylamines, indole-2,3-diones and maleic anhydride, through the hetero Diels-Alder reaction involving an imine intermediate (Scheme 54).[199] It was also demonstrated that ultrasound irradiation was quite efficient for the imino Diels-Alder cycloaddition, leading to increased yields and shorter reaction times compared to conventional heating.

Copper catalysis in liquid PEG-400 allowed to access one-pot fused pyranones via a cross-coupling reaction between 3-iodothiophene-2-carboxylic acid with terminal alkynes, followed by a cyclization reaction (Scheme 55).[200] In silent conditions the reaction did not proceed. Moreover, even after prolonged heating, only moderate yields were obtained, when PEG-400 was replaced by other solvents (EtOH or *n*-BuOH).

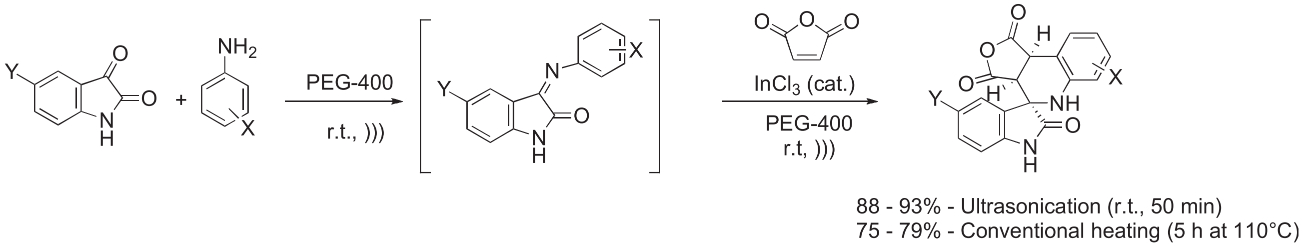
The reactivity of polymer-tagged substrates using US has been investigated in the past,[25,33,201] but only one example is reported on the use of melted polymers to perform organic syntheses.[39] The ligand-free, copper-catalysed cyanation reaction from aryl halides was performed using non-poisonous, inexpensive potassium hexacyanoferrate(II) K4[Fe(CN)6], both a food additive and cyanide source, in melted PEG-5600 (Scheme 56).[39]

Sonication was performed at 80 °C, to allow the polymer to be homogeneously melted, in a pulsed fashion (20 min reaction, corresponding to 10 min sonication) to avoid catalyst deactivation.[202,203] Conversion and yield were strictly dependent on the PEG molecular weight. Considering that the ability of the medium to absorb acoustic energy also depended on the viscosity of the medium, an increase in the melt viscosity (markedly dependent on the molecular weight in the case of PEGs) enhanced the absorption of acoustic energy and, consequently, determined a more efficient energy-transfer to the molecules. No conversion of the starting material was observed with low molecular weight PEGs (PEG-200, PEG-300 and PEG-1100). Melted PEGs with a molecular weight higher than 6000 Da and up to 20000 Da were too viscous to allow efficient diffusion of the reactants. PEG-5600 displayed the best results, although the catalyst was deactivated after the first run (aggregation of Cu-NPs formed during the US-promoted polyol process, formation of stable Cu$_2$[Fe(CN)6] complexes, with high affinity of cyanide ions toward copper-based catalysts).

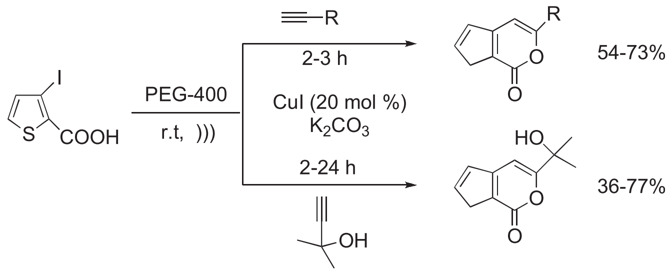
Cavitation or mechanochemical effects were evoked to explain the reactivity of the system, excluding an activation due to thermal effects. Indeed, when microwaves were applied (at 160 °C), using palladium, silver or copper salts, the reaction did not proceed. Moreover, compared to literature reports, a significantly lower amount of copper catalyst was used (5 mol% instead of 10–30 mol %) compared to irradiation under microwave activation in other solvents, with leaching into benzonitrile products below the threshold levels for human copper intake.

Liquid PEG polymers were also used in combination with organoelements (S and Se) to access highly substituted aminothiophenes,[204] thioureas[205] and selenopyridines[205] (Scheme 57). In all cases, the use of sonication increased the reaction yields, and decreased the reaction times, compared to silent conditions under stirring or using microwaves. The reaction failed when performed in organic solvents (EtOH, ACN, THF, Toluene, CHCl$_3$, DES, glycerol, etc.) or in neat conditions. In the case of thiourea preparations only water performed similarly than PEG.

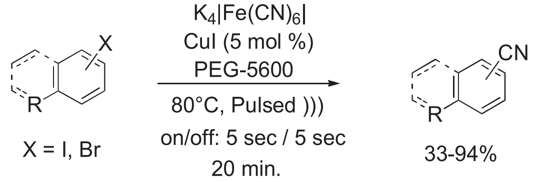
An equimolar mixture of water and PEG-400 was affective for the US-promoted preparation of highly substituted pyrazoles via a three components reaction from aldehydes, malononitrile and substituted hydrazines (Scheme 58).[206] Similar results could be obtained either by grinding the mixture in neat conditions or by



Scheme 54. Spiroquinoline synthesis with high atom-economy.



Scheme 55. One-pot two step synthesis of pyranones.



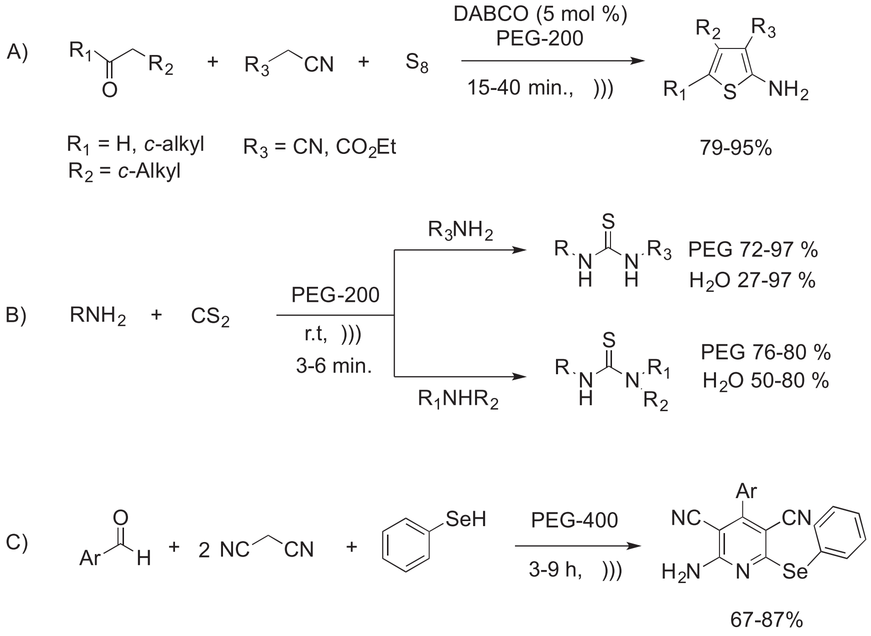
Scheme 56. Cyanation reaction under pulsed sonication in melted PEG.

using *n*-butyl imidazolium hydroxide [BIMH][OH] as additive.

For the preparation of *N,N*-bis-(phenacyl)-aniline, yields were improved by increasing the amount of PEG-400 (more than because of ultrasound influence), outperforming compared to the reaction performed either by grinding in neat conditions or using EtOH as the reaction solvent (Scheme 59).[207]

The role played by the nature of PEG solvent is highlighted for the transformations given in Schemes 55–57 and 59. Conversion and yields were strictly dependent on the PEG molecular weight or its amount and the reaction failed when investigated in other solvents (DES, glycerol, aliphatic alcohols, etc.). The intensity of the ultrasound radiation at a distance l from the probe depends on the distance at distance zero and from the attenuation coefficient α (*c.f.* equation at page 2) which describes the strength of the propagation wave across the medium. This coefficient is strictly related to the shear viscosity of the medium η, being the other parameters of the equation constant (*i.e.*: with f the nominal frequency of the equipment, ρ the density of the medium and c the speed of sound). At high molecular weight, the high viscosity of the polymer could inhibit the reaction because of poor mass transport, while low molecular weight PEGs could not be efficient in terms of viscosity, resulting in poor attenuation coefficient α, provoking poor cavitation. This can also explain why some reactions performed in PEG-water mixture failed under US, due to diminished viscosity of the reaction mixture in the presence of water.

EG and its polymers were frequently used for the preparation of nanoparticles or nanosystems, taking into account both its stabilizing and capping properties. For instance, 3D flower-like bismuth sulphide nanostructures were obtained by high-intensity sonication (24 kHz, 400 W/cm^2 probe) of an EG solution of $Bi(NO_3)_3 \cdot 5H_2O$ and $Na_2S_2O_3$ precursors, in the presence of CTABr as a surfactant.[208]



Scheme 57. Organoelements in PEG to access heterocycles and thioureas.

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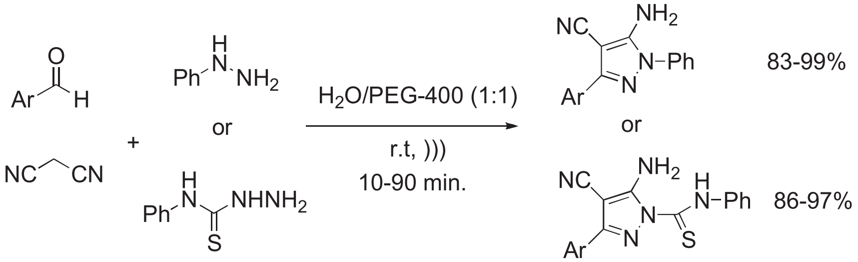
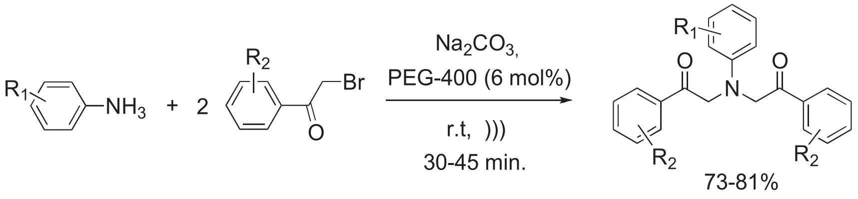


Scheme 58. Cascade reaction to pyrazole.



Scheme 59. Substitution reaction in PEG.

Sonication proved to be essential for the reaction rate enhancement, but also for the formation of flower-like Bi_2S_3 superstructures. Indeed, larger aggregates of rod-like particles were predominantly observed when the synthesis was repeated under conventional stirring (Fig. 14a–c). Moreover, the morphology was strongly influenced by the choice of the solvent: when acetyl acetone or DMSO were added to EG, the product consisted in 1D rods with a low or high aspect ratio, respectively, but no 3D superstructure could be observed.

EG was used as a polyol-type solvent for the surfactant-free sonochemical conversion of Fe(II) and Fe(III) precursors to hydrophilic magnetite nanoparticles under basic conditions.[209] The authors suggested that EG efficiently modified the surface of particles that were stable against aggregation for months in a hydrophilic solvent like ethanol. US intensity played also a pivotal role in determining the final properties, since magnetite nanoparticles, obtained under optimized conditions (*i.e.* 30 min with a 20 kHz, 35 W/cm^2 probe reactor), showed a markedly increased stability with respect to samples obtained with other applied intensities.

Sonication of an EG solution of $SnCl_2$, carried out with a probe reactor under N_2 atmosphere, promoted the uniform decoration of multi-walled carbon nanotubes (MWCNTs) with crystalline tin nanoparticles (3–5 nm diameter).[210] Notably, it was underlined by the authors that the locally extreme conditions due to cavitation were responsible for the reduction of Sn(II) to metallic nanoparticles, via the polyol process, which would be energetically unfavourable in EG in reflux conditions. Similarly, 30 kHz US irradiation of a palladium nitrate EG solution containing poly(vinyl pyrrolidone) (PVP) produced spherical Pd nanoparticles (average diameter of 5 nm) efficiently stabilized by the coordination of the metallic surface by the C=O groups distributed along the polymer chain.[211]

Examples of bimetallic alloy Pd$_n$M ($n = 1$ for M = Mn, Fe, and Co; $n = 1$, 2, and 3 for M = Ni) nanoparticles for electrochemical applications were also synthesized on carbon supports, by sonochemical reactions of $Pd(acac)_2$ with $M(acac)_2$ (M = Ni, Co, Mn) or $Fe(acac)_3$, in EG.[212] A 500 kW US generator (20 kHz with a 13 mm probe) with 30% amplitude was applied for 3 h under an Ar environment at room temperature. The obtained nanoparticles presented comparable diameter (7–8 nm) and the same crystalline structure. By XRD studies, the authors described in detail the nanoparticles. and the absence of any XRD signal than that of the palladium is a demonstration regarding the incorporation of M inside the Pd lattice (Fig. 15).

In the sonochemical reduction of nickel nitrate or cobalt nitrate to spherical Ni- or Co-nanoparticles carried out with a 20 kHz probe

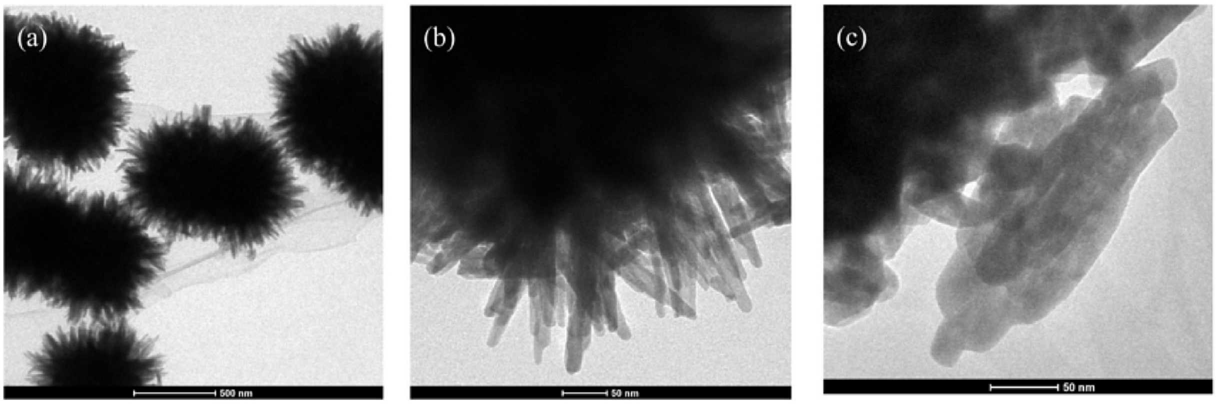


Fig. 14. Bismuth sulphide nanostructures obtained in EG by high-intensity sonication (a: scale = 500 nm; b: scale = 50 nm) or by conventional stirring procedure (c: scale = 50 nm) (Image reproduced from reference 190, by kind permission of Sociedade Brasileira de Quimica, PubliSBQ).

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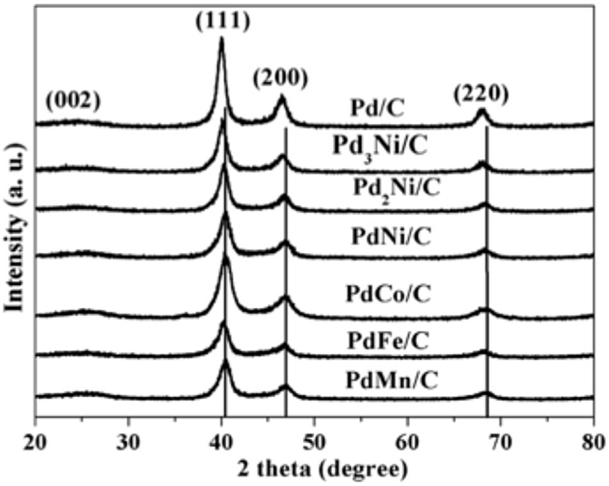


Fig. 15. XRD patterns of Pd/C and Pd_nM/C samples (Image reproduced from reference 194, by kind permission of Elsevier).

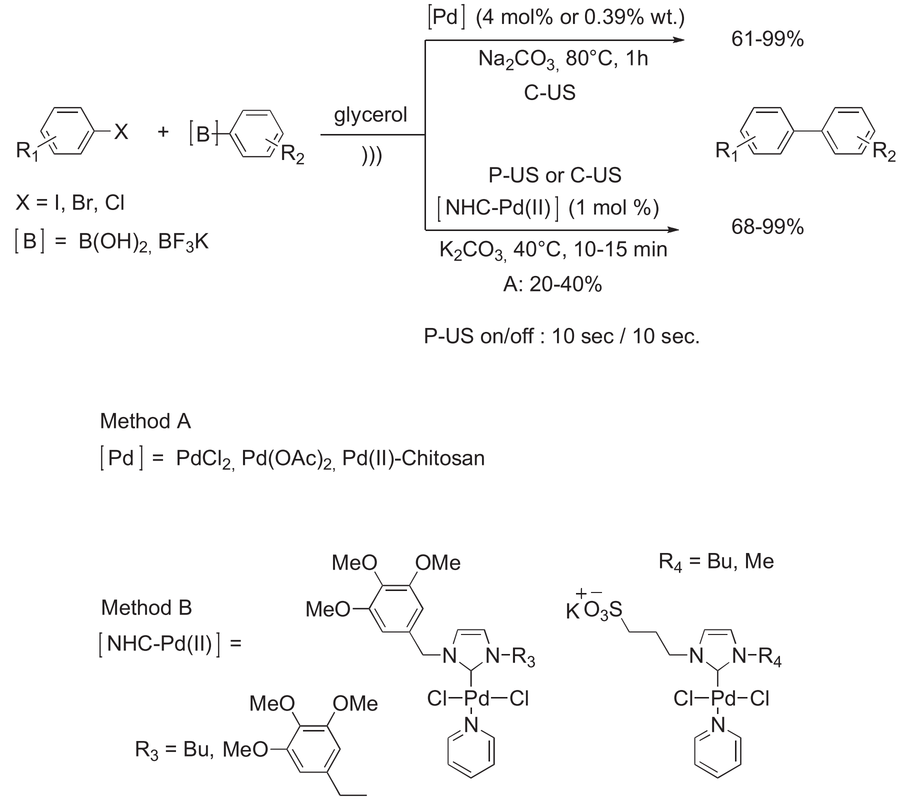
reactor, TEG and PEG-400 outperformed EG, when used as solvents and stabilizers.[213] More precisely, while particles obtained in EG showed large diameters of *ca.* 50 nm (Ni) and 350 nm (Co), as well as a tendency to precipitate shortly after reaction, particles obtained in PEG-400 proved to be very small (3.2 nm and 2.3 nm respectively), and extremely stable towards aggregation and flocculation, while particles obtained in TEG had properties somehow in-between. These beneficial effects derived from the superior viscosity of PEG constituted an efficient physical barrier to nanoparticle growth after nucleation. Interestingly, the authors repeated the preparation applying an external magnetic field during the growth of the ferromagnetic particles. They found that nanowires were formed in the place of spheres. Apparently, the extreme conditions produced by cavitation did not hamper the particle motion and growth driven by magnetic interactions. This could stem from the fact that sonochemical reactions involving ionic species took place in the less energetic liquid surroundings of cavities rather than in the vapour phase inside the cavity itself.

EG- and EG oligomers-phase sonochemical syntheses of inorganic nanosystems are rather abundant. Further examples include the preparation of ‘taper-shaped’ HgSe nanorods from $Hg(OAc)_2$ and Se powder,[214] as well as the conversion of $Cu(OAc)_2{\bullet}H_2O$ and elemental sulphur into copper sulphide hexa-nanoplates and nanoparticles.[215] Nevertheless, several other solvents have been successfully combined with the use of US reactors.

4.2. Reactions in glycerol

Glycerol, produced as non-hazardous waste by the biodiesel industry from the transesterification of vegetable oils, is attracting increasing interest as a green solvent, due to its low cost, wide availability and biodegradability. It constitutes a valuable medium for sonochemistry, taking into account its favourable physical properties such as very low volatility, no flammability, high boiling point, and proper viscosity. It displays excellent acoustic cavitation even at high temperatures (70–100 °C or more), which is negligible for ultrasound-promoted reactions in water.

The use of glycerol for many industrial and pharmaceutical preparations, and as a sustainable solvent in liquid-phase catalytic and non-catalytic organic transformations, is already well documented in the literature. It present numerous advantages leading to improved products yields and selectivity, easy separation of products, re-use of the solvent and/or catalysts easily recycled, formation of a polyol system for nanoparticles synthesis and stabilisation.



Scheme 60. Suzuki-Miyaura cross-coupling reaction under continuous (C-US) and pulsed sonication (P-US).

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However, it is also associated to some drawbacks, including intrinsic reactivity of the polyol backbone, poor solubility for highly hydrophobic organic compounds, high viscosity responsible for poor mass transport at room temperature or mild heating, which limit its use in some organic transformations. However, although sonication is one of the ways to overcome these limitations, only a few numbers of papers describe the use of glycerol in ultrasound promoted transformations. A major focus relies on C—C bond formation by metal-catalysed processes such as Pd-mediated Suzuki-Miyaura coupling,[202,216] Ir-[203] or Ru-mediated[216] transfer hydrogenation (TH), Ru-based ring closing metathesis (RCM) in glycerol micelles,[49,217] Zn-mediated Barbier reaction[216] and Nb-catalysed electrophilic substitution.[218] In all cases glycerol proved to be a greener, less expensive, and safer alternative to the classic volatile organic solvents. This also applied for Cu-NPs preparation,[219] while ultrasound was efficient for rate acceleration, favouring nanoparticle's formation.

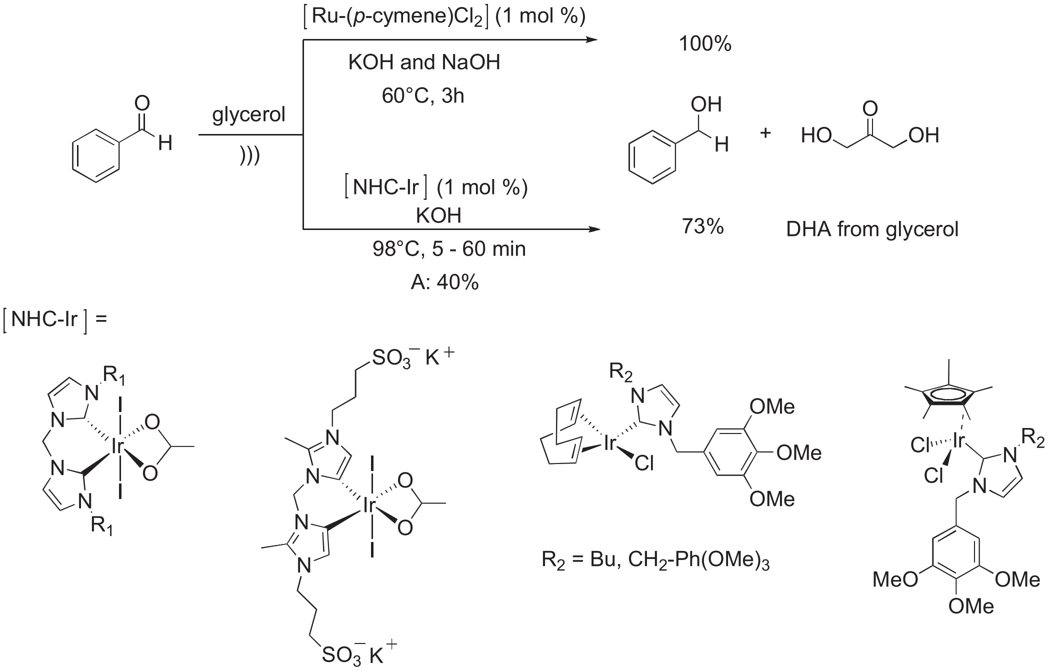
Ligand-free Suzuki-Miyaura reaction in glycerol was investigated with commercially available ($PdCl_2$, $Pd(OAc)_2$),[216] chitosan-supported[216] (Method A) or *N*-heterocyclic carbene (NHC)-Pd(II) precatalysts (Method B),[202] under continuous (C-US) or pulsed (P-US) sonication. The last one allowed modulation of the sonication strength, hampering catalyst deactivation, dehalogenation or deboronylation of substrates, by avoiding temperature increase during the process (Scheme 60).

A the comparative study using ultrasound, microwave and simultaneous microwave-ultrasound irradiation (SMUI), led to improved reaction rates and comparable yields in the experimental conditions reported in Method A.[216] The Pd(II)-chitosan supported catalyst was also the most suitable for cross-coupling reaction using arylchlorides. In Method B,[202] the reaction conditions were adapted according to the arylhalide/boron reactant combination. When $PhBF_3K$ was used, the reactivity and yield depended on the irradiation mode and the amplitude (A) of sonication: values of 20% for continuous sonication (C-US) or 40% for pulsed sonication (P-US) led to comparable results. The outcome of the reaction was not dependent on the amplitude when using the more stable $ArB(OH)_2$. As a general trend, at lower amplitude values (10%), the homocoupling product was observed, while the extent of deboronylation and dehalogenation increased at high amplitude values under C-US. NHC-Pd(II) precatalysts performed better than commercially available $[PdCl_2(IPr)Py]$, $Pd(OAc)_2$ and $Pd(PPh_3)_4$, with full conversion of substrates in shorter reaction times, lower catalyst loading and milder temperature than in previous reports. Compared to heating in an oil bath, P-US activation displayed kinetics two twice faster. Although recycling was not effective probably because of leaching or catalyst deactivation, NPs were also formed. Under P-US activation, the nanoparticle's average size (3–4 nm, 5–7 nm or 17–21 nm) was dependent on the catalysts/substrates combination, while XPS analyses showed the presence of reduced palladium surrounded by the NHC ligand having the sulfonate groups. Moreover, NPs obtained under continuous mode were less homogeneously dispersed than those coming from a pulsed ultrasound method, supporting the experimental evidence for a more efficient catalytic process in these conditions.

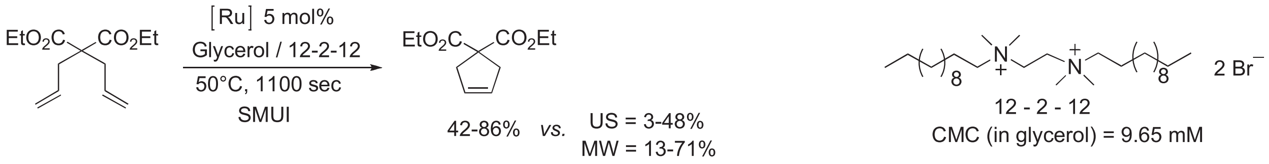
The dual role of glycerol as both the reaction solvent and hydrogen source in the transfer hydrogenation (TH) reaction on benzaldehyde using low loading of Ru- or NHC-Ir(I) and bidentate NHC-Ir(III) catalysts, was also investigated (Scheme 61).

Sonochemistry achieved with a titanium horn using Ru(*p*-cymene)Cl_2 dimer as catalyst, led quantitatively to benzyl alcohol after 3 h, compared to a combined US/MW irradiation by means of a pyrex horn (84% yield), or using an oil-bath (66% yield after 12 h).[216] The enhanced kinetics (and yields) under sonication was also explained by an optimal base dispersion in glycerol.

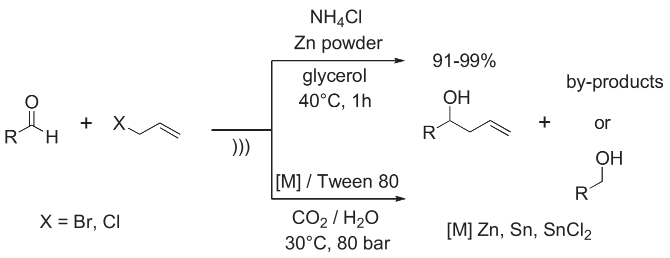
It was also demonstrated that the Ir-catalysed TH reaction on benzaldehyde (for 5 min) under sonication in glycerol, outperformed compared to an oil-bath heating (11% after 30 min). In the case of acetophenone sonication (30 min at 40 °C using 1 mol% of catalyst, yield 56%) a lower yield was obtained compared to oil bath heating (7 h at 120 °C, using 2.5 mol% of catalyst, 77% yield). However, the reactivity of substrates was strictly dependent on the catalyst used. Better yields of benzyl alcohol were obtained using NHC-Ir(I)-catalysts, while bis-chelating abnormally bound NHC-



Scheme 61. Ru- and Ir-catalysed transfer hydrogenation reaction from glycerol.



Scheme 62. RCM in glycerol micellar conditions.



Scheme 63. Barbier reaction for allylation.

Ir(III) catalyst was more adapted for the synthesis of 1-phenylethanol (56% yield). Both the catalyst solubility in glycerol, and the sonication setting parameters influenced the course of the reaction. In the case of acetophenone, TH led to lower yields (21%) of the corresponding alcohol, when the amplitude was 20% instead of 40%. The catalytic system could not be recycled, and spherically shaped Ir(0)-NPs were formed within 5 min with a narrow size distribution of *ca.* 3–5 nm.

Glycerol was also explored as solvent for micellar catalysis (achieved with dicationic surfactants).[49,217] The ring closing metathesis (RCM) of diethyl diallylmalonate (DEADAM) using SMUI was investigated with various Ru-benzylidene and Ru-indenilydene catalysts, and the results compared with the reaction performed under ultrasound and microwaves (Scheme 62).

It was demonstrated that SMUI generally led to better yields of cyclized products, especially compared to the use of only ultrasounds. Moreover, micellar conditions prevented the formation of isomerised by-products during RCM, which is usually due to the presence of Ru-H species formed *in situ* when protic (alcoholic) solvents are used. In this case, micelles act as a protective environment, hampering glycerol reactivity. In contrast, the SMUI hybrid technology, which provides efficient heating of glycerol under MW irradiation and efficient mass transport by cavitation, allows to overcome all the drawbacks described so far by using glycerol as the reaction solvent.

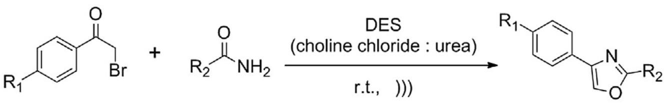
High intensity ultrasound activation was also efficient for the zinc-mediated Barbier reaction, an important route to access homoallylic alcohols (Scheme 63).[216,220] When sonication was achieved by a tip horn, instead of a cleaning bath in the classical solvent system THF/NH_4Cl, the allylation of benzaldehyde affords quantitatively the corresponding addition product, with no formation of by-products.[216]

The Barbier reaction was also described in *sc*-CO_2, in the presence of a polar medium, specifically an aqueous phase (30 °C, 80 bar) (Scheme 63).[220] To increase both the yields and the reactions rate, the authors used a Tween 80 as additive and a modulated-amplitude sonochemical procedure. In particular, the presence of Tween 80 contributed to reduce the competing aldehyde reduction increasing, as a consequence, the reaction chemoselectivity. For the sonication, a 20 kHz −1500 W processor, coupled to a titanium alloy horn with tip diameter 1.9 cm was used. The setting amplitude could be varied from 20 to 80%, while the pulse rate was 25% (1 s on/3 s off), in all experiments. Through a calorimetric calibration, the intensity of the acoustic power dissipated to the fluid was evaluated as approximately 70 W/cm^2.

Another example involved the use of pulsed sonication (P-US) for the preparation of spherical Cu_2O nanoparticles of 80–150 nm, from copper acetate and glycerol.[219] Indeed, the significance of sonication was highlighted since no NPs were formed in silent conditions. Cu_2O NPs were successfully tested for the *N*-arylation of imidazole in DMSO, upon classical heating. Ultrasound accelerated C–N bond formation. So was the copper-catalysed (CuI, 10 mol%) C–S cross-coupling reaction between 2,5-dimethoxy-iodobenzene and thiophenol in glycerol (1 h instead of 24 h in silent conditions), leading to comparable yields (88%). However, the study was limited to only one example.[221]

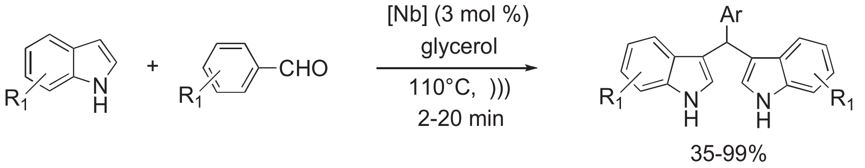
C–C bond formation was also possible by the niobium-catalysed preparation of bis(indolyl)methane in glycerol, under sonication. The electrophilic substitution of indoles with carbonyl compounds was achieved using cheap, easy to handle and non-toxic, ammonium niobium oxalate (ANO) $NH_4[NbO(C_2O_4)_2(H_2O)x]\cdot nH_2O$ as catalyst (Scheme 64).[218] It was deactivated after the first run, while glycerol could be recycled for four further runs, adding a new ANO for each reaction.

In a different approach, glycerol was used, not as solvent or



a (R_1 = H, R_2 = NH-C_6H_5): 86%; energy saving = 87%
b (R_1 = Br, R_2 = NH-C_6H_5): 89%; energy saving = 85%
c (R_1 = NO_2, R_2 = NH-C_6H_5): 90%; energy saving = 88%
d (R_1 = NO_2, R_2 = CH_2CN): 83%; energy saving = 86%
e (R_1 = NO_2, R_2 = *p*-NO_2-C_6H_4): 82%; energy saving = 86%

Scheme 65. Energy saving during oxazole's synthesis under ultrasounds.



[Nb] = $NH_4[NbO(C_2O_4)_2(H_2O)_x]\ nH_2O$ **(ANO)**

Scheme 64. Synthesis of bis(indolyl)methanes via electrophilic substitution of indoles.

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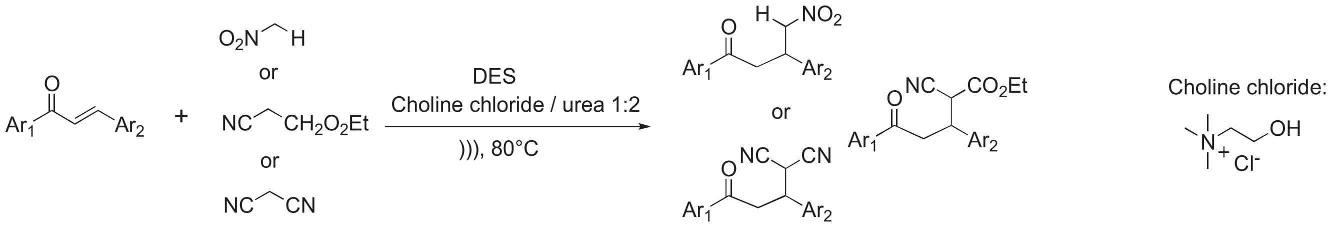


Scheme 66. Addition reaction in DES.

reactants, but as substrate, undergoing triacetylation reaction with acetic anhydride, catalysed by clays such as Montmorillonite K10 or KSF, in heterogeneous conditions.[222] After 20 min sonication, the yield of the corresponding acetylated product depended on the clay that was used, better results being obtained with KSF compared to K10 (55% and 79% yield respectively), due to the higher acidity of KSF, as claimed by the authors.

4.3. Reactions in deep eutectic solvents (DESs)

The use of a deep eutectic solvent obtained from choline chloride and urea $[Me_3N(CH_2)_2OH][Cl]$, which was mentioned earlier in this review in a comparative study with water and liquid PEG,[73] was also reported for the synthesis of oxazole compounds from phenacyl bromide derivatives and substituted amides, under sonochemical conditions (Scheme 65).[223] DESs retain most of the beneficial properties of ILs and add a number of attractive features such as easy and cheap preparation, biodegradability and non-toxicity. Moreover, the use of US irradiation (22 kHz, 750 W probe reactor) afforded high yields and reaction rates, with a drastic reduction in energy consumption relative to conventional thermal heating, as calculated by the authors for each screened substrate (Scheme 65, a–e).

A green protocol for the efficient synthesis of β-functionalized ketone derivatives is achieved with the combination of ultrasound and the DES choline chloride–urea (1:2 ratio) (Scheme 66).[224] Under optimized conditions, nucleophilic attack of the active methylene on α,β-unsaturated ketones gave the conjugate addition product within 40–50 min in excellent yields (89–95%). Similarly to ILs, choline chloride-urea played the double role of both solvent and catalyst. This is an advantage since this DES is particularly suitable for a several time re-use, without loosing its peculiar characteristics. An apparatus equipped by a horn (titanium steel tip of 13 mm), and with an output power of 750 W, was used as US source (intensity of 227 W/cm^2, frequency of 20 kHz).

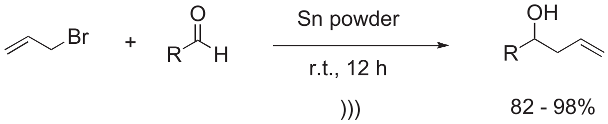
Commercial rapeseed and corn oils were used as green and safe solvents (both are edible products) for the US-promoted synthesis (20 kHz, 600 W probe sonicator) of highly magnetic iron nanoparticles with notable stability towards air oxidation.[225] These vegetable oils represent good alternatives to the most common solvents used in sonochemistry, as they meet the fundamental requirement of low volatility. However, a partial polymerization was observed during US irradiation, due to the presence of several unsaturated fats. This degradation, although hampering their re-use, favours the formation of a stabilizing matrix for the iron nanoparticles, which proved to be a very effective barrier against oxidation of the metal surface. Indeed, poly-unsaturated rich corn oils afforded better results compared to mono-unsaturated rich rapeseed oils.

4.4. Reactions in subcritical CO_2 (sc-CO_2)

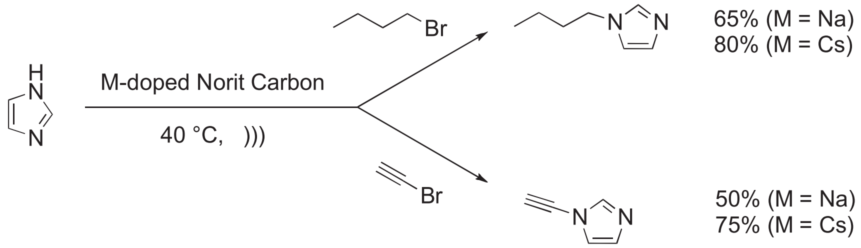
The ultrasound-activated reaction described in the previous sections were investigated at atmospheric conditions. A still unexplored niche in sonochemistry having high potential of innovation is the ultrasound-promoted cavitation at increased pressures. If the formation of bubbles in a liquid can be hampered by an increase of the static pressure, example of cavitation in liquid CO_2 and in supercritical conditions are reported. The Barbier reaction has already been described in Scheme 61. However, the use of supercritical fluids in US-promoted reaction is not still fully exploited. Only polymerization reactions were investigated. More than ten years ago, a remarkable paper described the catalyst-/initiator-free methyl methacrylate (MMA) radical polymerization to PMMA, by using a probe sonicator coupled to a high pressure cell containing liquid CO_2 as solvent, at 75 bar and at a 10 °C (Fig. 5l).[226] As pointed out by the authors, it was not necessary to overcome the critical point of the gas since, once the phase boundary between liquid and vapour was lost, cavitation could not physically take place. Moreover, an US intensity of 25 W/cm^2 was not sufficient to induce cavitation and 125 W/cm^2 was needed. High molecular weight PMMA was obtained through an overall clean procedure. Nonetheless, this interesting technique has not gained substantial popularity over time, probably due to the reactor complexity and difficult scalability.

5. Solventless sonochemical reactions

The absence of solvents is a highly desirable asset for an environmentally friendly chemical synthesis, since large volumes of wastes along with process complexity, are often reduced significantly. Not every reaction can be carried out in solvent-free conditions, the physical properties of reactants must satisfy specific requirements. This is particularly true when US irradiation is employed, taking into account the strong influence of viscosity, the density, the thermal conductivity and many other parameters acting on the efficiency of acoustic absorption and mass transfer. Bulk reactions avoid the transmission of the mechanical energy resulting from cavitation to the molecules of solvents. Consequently, it is easier to supply energy to the reactants at a higher rate compared to the loss, which is due to thermalization processes. Similarly to the case of mechanochemical reactions, this excess of energy can promote physico-chemical transformations including vibrational and electronic excitation, bond deformation and cleavage or atom migration.[25] Taking into account these unique features, an impressive number of sonochemical organic syntheses, as well as some polymerization reactions, were successfully achieved in solvent-free conditions, during the last decade. Most of the reaction described in this section are usually supported on a solid surface (materials or metals). The effect of shockwaves, usually



Scheme 67. Sn-mediated allylation reaction.



Scheme 68. Imidazole alkylation reaction in heterogeneous conditions.

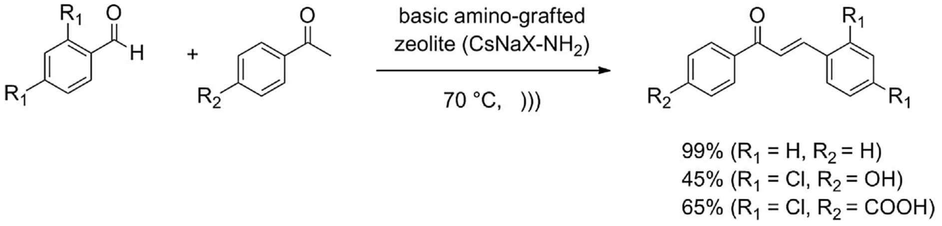
more prominent than microjets, are responsible of diverse structural changes. Fragments were obtained from friable materials, deformation occurred on ductile materials, while exfoliation was produced from layered ones, as for graphene and similar contemporary materials. Indeed, graphene prepared by sonication showed improved physical and chemical properties compared to preparation by conventional methods. It was previously underlined that passivated layer were removed from metal surface by action of ultrasound (*e.g.* Li, Mg or Na). However, depending on the metal, other phenomena can occur, such as fragmentation, mainly observed for high melting point metals, or coalescence for low melting point metals (*e.g.* Zn or Sn). Moreover, changes in size and morphology can also be observed for metal micro- and nanoparticles, catalytic activity can be modified, while amorphous solids can evolve to a well-defined crystalline state. However, this is not general trend: tungsten micro-particles were not modified upon sonication. The reader can refer to excellent reports,[15,27] addressing the individual and mutual effect of input parameters in the nanomaterial synthesis or structural modification of metal surfaces upon sonication.

The physical state of the reactants can be liquid or solid. In the case of liquid reactants, the operating temperature has to be kept below their boiling point, while solid reaction mixtures at room temperature can be sonicated only as melt. Hence, the operating temperature will correspond to the melting point of one of the reactants (and in any case it is kept below their boiling points), which may also act as solvent for the reaction. As previously discussed for solvents, also in the case of neat reactions, the combined effect of the intrinsic properties of the mixture, such as viscosity, vapour pressure and surface tension for a well-defined liquid/liquid system or melt, are associated to specific heating profiles during sonication.

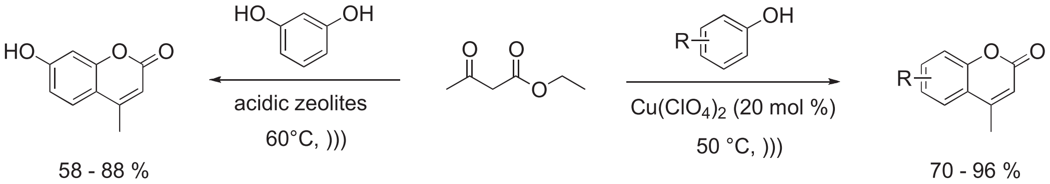
5.1. Solvent-free (neat) organic reactions

Tin-catalysed homoallylation reactions were performed in bulk, by addition of aldehydes to a suspension of Sn powder in excess, allyl bromide, followed by sonication for 12 h (unfortunately, the US equipment was not indicated) (Scheme 67).[227] Yields were comparable to those achieved in water or IL solvents, starting from both aromatic and aliphatic aldehydes. However, ketones could not be converted due to the lower reactivity of the carbonyl group. The significance of sonication was evaluated by comparison with conventional stirring for both the formation of the allyltin bromide intermediate and the subsequent allylation reaction. As a result, US irradiation proved to be unequivocally necessary for the first step (probably due to the activation of the Sn surface), while it contributed only slightly to the subsequent formation of the Sn alkoxide. It was underlined that, unfortunately, significant amounts of toxic allylstannane compounds were formed, thus limiting the method for the synthesis of fine chemical.

The solvent-free N-alkylation of imidazole with 1-bromobutane, catalysed by Na^+- or Cs^+-doped Norit-carbon (Scheme 68) under both sonochemical (40 kHz, 550 W Cleaning bath) and thermal conditions, was described by Martin-Aranda.[228] By using the more active Cs^+-Norit, the US rate enhancement was evident after 120 min at 40 °C (80% *vs.* 45% yield), but become even more evident when the reaction was performed at 20 °C (71% *vs.* 25% yield), since lower temperatures decreased the liquid phase vapour pressure and, consequently, increased the energy released by each cavity collapse. Afterwards, the same US equipment and a very similar procedure was employed for the synthesis of *N*-propargyl imidazole, from imidazole and propargyl bromide (Scheme 68). Similar observations with respect to the synthesis of *N*-butyl imidazole were reported by the authors.[229] Moreover, the aforementioned



Scheme 69. Claisen-Schmidt condensation in heterogeneous conditions.



Scheme 70. Homogeneous or heterogeneous Pechman condensation in neat conditions.

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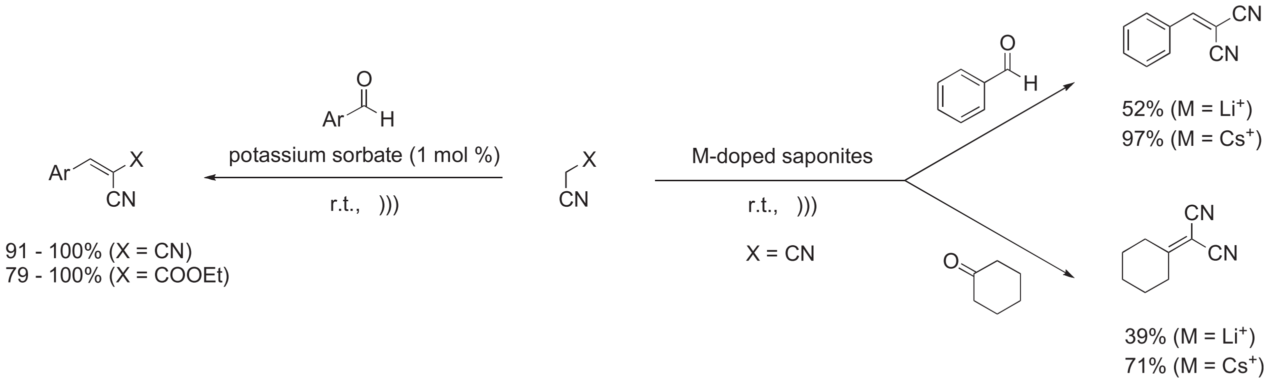


Scheme 71. Neat Knoevenagel condensation over metal-doped saponites or potassium sorbate catalysts.

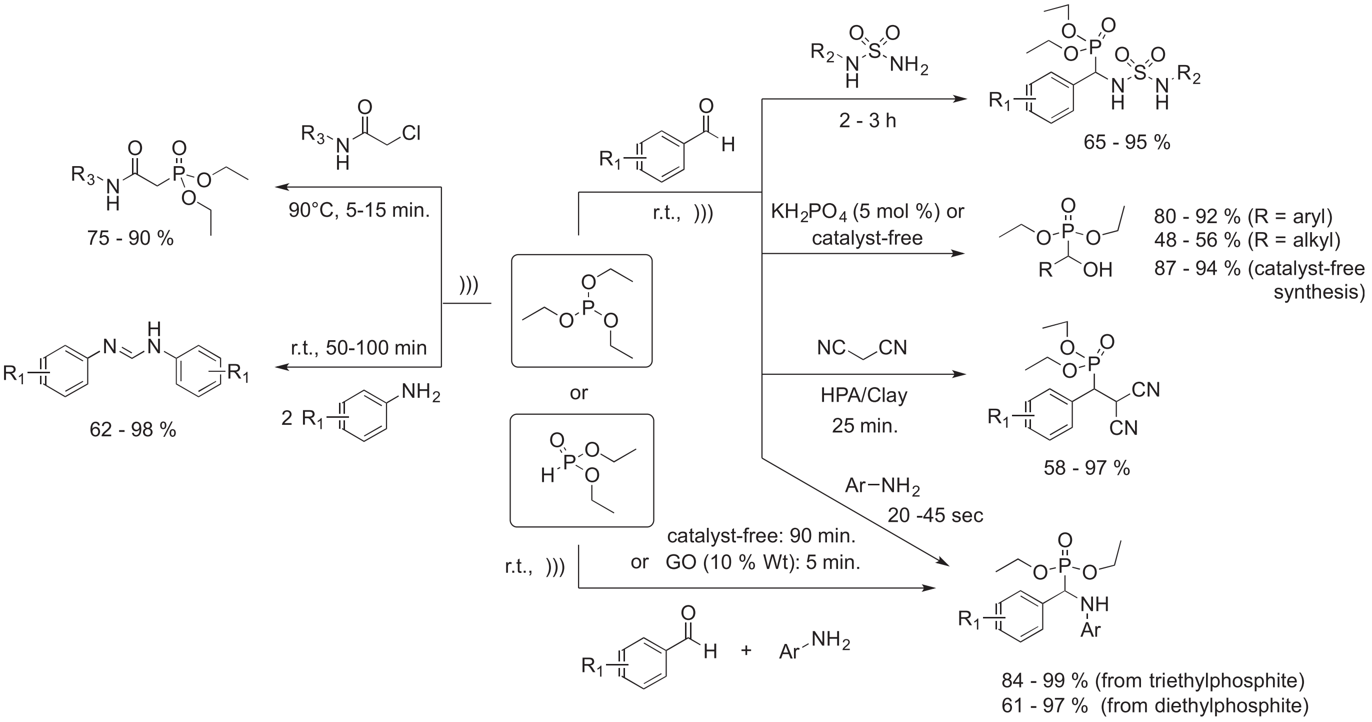
alkylation reaction with 1-butylbromide was modified by replacing carbon-based catalysts with Na- and Cs-exchanged X-zeolites grafted with NH_2 groups.[230]

The same group of investigators described the preparation of chalcones via the bulk Claisen-Schmidt condensation of aromatic aldehydes and acetophenone derivatives, catalysed by amino-grafted zeolites (Scheme 69).[231]

The obtained hydroxy- and carboxy-substituted chalcones synthesized only with low conversion values (13% and 46% respectively) when the conventional method is applied (*i.e.* NaOH/EtOH reflux for 18 h), exhibit interesting antibacterial activity. The zeolite-catalysed procedure produced similar conversions when the reaction was thermally activated (20% of hydroxyl- and 35% of carboxy-functionalized chalcones), but when sonication was applied better results were obtained (45% and 65% conversion respectively). In an analogous study, the condensation between benzaldehyde and acetophenone was performed using alkaline-doped Norit carbon as catalyst. A marked rate increase under sonochemical conditions compared to thermal activation (60% *vs.* 30% conversion for Cs-doped Norit carbon and 45% *vs.* 25% conversion for Na-doped Norit carbon, after 2 h at 20 °C).[232]

An evident and general yield increase was reported also in the case of the acid zeolite-catalysed Pechman reaction for the synthesis of hymecromone from resorcinol and ethyl acetoacetate (Scheme 70).[233] The positive effect of sonication compared to thermal activation proved to be independent of any other screened parameter, of the catalyst nature (Mordenite, zeolite Y, zeolite Beta or ZSM-5), of the catalyst amount, and of the resorcinol/ethyl acetoacetate molar ratio. As an example, hymecromone was obtained in 88% yield (62% under thermal activation) when 10 mmol of resorcinol and 20 mmol of ethyl acetoacetate were converted, in the presence of 0.3 g of Mordenite at 60 °C.

The use of copper perchlorate is as an efficient heterogeneous catalyst for the Pechman condensation of phenolic compounds with ethyl acetoacetate to obtain coumarins in the absence of solvent[234] (Scheme 70). A relatively high molar ratio of $Cu(ClO_4)_2$ proved to be necessary to obtain good yields. Sonication (35 kHz US cleaner) was a crucial requirement for short reaction times and higher yields of coumarins, as indicated by an accurate comparison under silent conditions, at variable catalyst loading. The latter catalyst and reaction set-up were employed by the same group to promote the solvent-free condensation of 2-naphthol, with urea or



Scheme 72. Multi-component phosphorylation reactions.

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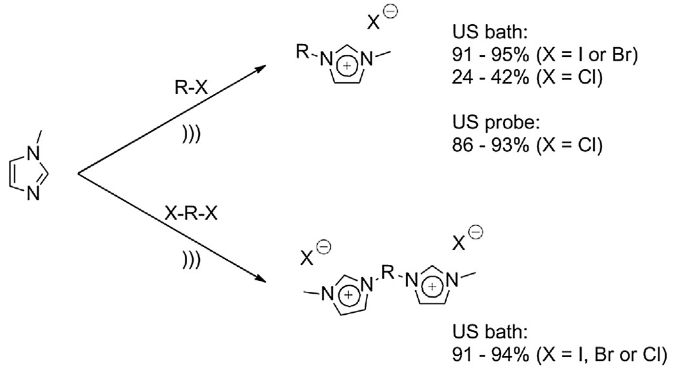
amides and aromatic aldehydes, to obtain amidoalkylnaphtols via a sonochemical, environmentally friendly procedure.[235] The Fe-catalysed Pechman reaction was also studied using $FeCl_3$ (10 mol %) in ultrasound-assisted solvent-free conditions, yielding 4-substituted coumarines.[236] By comparing experiments issued from either sonication (room temperature, 20 kHz, 130 W nominal power) or thermal reactions (70 °C), similar results were obtained (yields 40–99%). Coumarins could also prepared using solid poly(4-vinylpyridinium) hydrogen sulphate (10 mol %) in neat conditions.[237] Almost quantitative conversion of the reagent with 100% of selectivity, was obtained by irradiation for 5 min (35 kHz, 200 W), at room temperature, after 2 h. Under silent conditions, only 48% of yield was obtained. Conversion was noticeably improved by rising the temperature to 70 °C for 1 h.

The heterogeneous catalyst Cs^+-saponite proved also its efficiency in the Knoevenagel condensation, under sonochemical conditions (Scheme 71). Due to the difference in the saponite basicity, when malonitrile was reacted with benzaldehyde rather than cyclohexanone (by analogy with the reactivity under conventional activation) in the presence of Cs-rather than Li-doped catalyst, the Knoevenagen product was obtained with higher efficiency.[238] Interestingly, the use of acetone as solvent slowed down the reaction, compared to the environmentally friendly solvent-free conditions. Moreover, when the reaction was performed under magnetic stirring instead of US irradiation, a noticeable drop in the yield was observed (*e.g.* 49% *vs*. 97% with benzaldehyde after 2 h in the presence of Cs-doped saponite).

More recently, the Knoevenagel reaction was carried out by Liu and co-workers[239] to obtain substituted olefins from various aromatic aldehydes and ethyl cyanoacetate or malonitrile, in the presence of potassium sorbate as a green, non-toxic catalyst. A cleaning bath (300 W) was operated at different acoustic frequencies, observing a peak of activity for 80 kHz. Under these experimental conditions, a general rate enhancement was observed compared to conventional stirring. However, the benefit was less evident in the case of some already fast malonitrile-based condensations. Furthermore, 1,2-disubstituded benzimidazoles and benzothiazoles were synthesized by a solvent-free sonochemical reaction, in the presence of 10 mol% $LnCl_3$ and other rare-earth metal chlorides as catalysts.[240]

Reagents like diethylphosphite or triethylphosphite were largely exploited in sonochemical conditions, to access diverse phosphonates (Scheme 72). The one-pot sonochemical synthesis of α-aminophosphonates from aldehydes, aromatic amines and diethylphosphite (Kabachnich Fields reaction) could be successfully accomplished by a solvent-free procedure, without any catalyst[241] (relying on a 40 kHz, 250 W cleaning bath as the US source), as well as in heterogeneous conditions catalysed by non-toxic graphene oxide (GO) materials acting as acidic promoter.[242] The catalyst-free preparation α-aminophosphonates was highly improved in terms of yields (84–99%) and reaction time (20 s) when triethylphosphite was used instead of diethylphosphite (Scheme 72).[243]

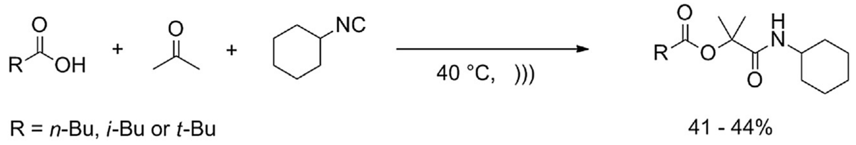
In catalyst-free conditions, as evidenced by the reaction of diethylphosphite or triethylphosphite with benzaldehyde at room temperature, sonication dramatically increased the rate of the three-components coupling (97% yield within 90 min *vs*. 18% overnight in silent conditions). However, heating to 70 °C was necessary even under US irradiation when less reactive ketones were chosen as substrates. While aniline derivatives proved to be smoothly converted, aliphatic amines (above all, secondary amines like piperidine) gave unsatisfactory yields or hardly any trace of the desired products. As proved by a recent study, under analogous conditions (35 kHz, 200 W, cleaning bath), the reaction could be significantly improved by the addition of either inexpensive 1-hexanesulfonic sodium salt[244] or *p*-toluenesulfonic acid (*p*-TSA)[245] as catalysts. α-Aminophosphonates could be prepared up to gram scale in GO-catalysed reactions, sonication improving both the reaction yield (94% under US *vs*. 79% in silent conditions at 80 °C) and kinetics (5 min *vs*. 4 h in silent conditions, with or without solvent), and the catalyst could be recycled several times (seven runs).[242]



Scheme 74. Preparation of ILs by alkylation reaction.

A similar sonochemical procedure was also developed for the synthesis of α-hydroxyphosphonates employing an US cleaning bath as the energy source, aldehydes, triethylphosphite, either in catalyst-free conditions[246] or using KH_2PO_4 as acidic catalyst[247] (Scheme 72). Solvent-free conditions proved to be not only the most environmentally favourable, but also optimal for the reaction efficiency. Indeed, the addition of an organic solvent produced a marked drop in the phosphonate yield (at least two-fold). On the other hand, no conversion could be observed with ketones (instead of aldehydes), either when using KH_2PO_4, or in the absence of catalyst.

The versatility of the methodology allowed the one-pot preparation of α-sulfamidophosphonates[248] by an ultrasound activated solvent-free three-components condensation reaction between triethylphosphite, an aromatic aldehyde and sulfonamide (Scheme 72). No reaction occurred in silent conditions for 5 h, while a quantitative conversion was achieved in a few minutes under US. The essential role played by ultrasound irradiation was also demonstrated for the preparation of β-malonophosphonates[249] using Keggin-type heteropoly acids (HPAs) such as $H_5PV_2W_{10}O_{40}10H_2O$ supported on clay, and also in the Arbuzov reaction for the preparation of various *N*-acylamines, *N*-acylaminoesters, *N*-acylaminoalcohols, *N*-acylsulfonamides,[250] and



Scheme 73. Passerini reaction involving hindered substrates.

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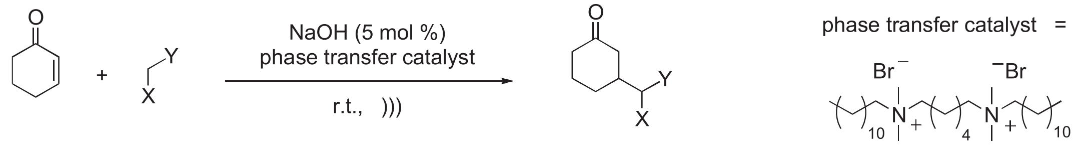
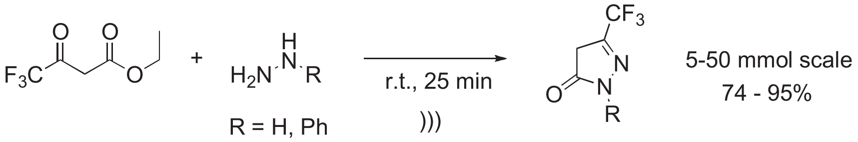


Scheme 75. Solvent-free Michael addition in PTC conditions.



Scheme 76. Catalyst-free condensation reaction to pyrazolones.

aldimine[251] (Scheme 72).

The Passerini reaction, another multi-component reaction, usually proceeding under high-pressure conditions when hindered substrates are involved, has been investigated in neat conditions. Indeed, the extreme conditions generated locally during cavitation accelerated the formation of α-acyloxyamides, without need of pressurized reactors. As an example, the model reaction involving acetone, cyclohexyl isocyanide and pentanoic acids, proceeded at room temperature in comparable yields, at a high pressure of 300 MPa for 16.5 h, and within 1 h under high-intensity sonication (Scheme 73).[252] The effect of the temperature was investigated, and indicated a maximum of activity at 40 °C (isonitrile decomposition was observed at higher temperature). Interestingly the role of US intensity was also assessed, a six-fold rate decrease was observed when the 1200 W probe reactor was replaced by a 100 W cleaning bath.

Namboodiri and Varma[253] utilized an US cleaning bath to carry out the synthesis of 1-alkyl-3-methylimidazolium halide ILs to efficiently mix such viscous products in the absence of solvent. Upon continuous irradiation for 2–4 h, *N*-methylimidazole reacted smoothly with several alkyl iodides and bromides. However, a high-intensity US probe was needed to successfully convert alkyl chlorides (Scheme 74). During sonication, the temperature raised from 25 °C to 40 °C when the less energetic cleaning bath was employed, while it reached 80–100 °C with the probe. Moreover, as the IL formed, the temperature increased to 115–125 °C due to the exothermic reaction. It is worth noting that these experimental conditions were suitable for the subsequent sonochemical Pd-catalysed Suzuki coupling, achieved by simple addition of reactants to the *in-situ* generated IL.

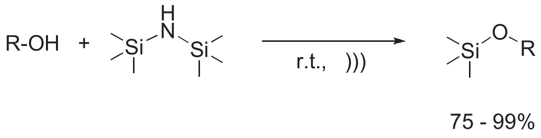
Similarly to RCM in glycerol micellar conditions (Scheme 62),[49,217] long-chain bis-cationic ammonium salts were used as phase-transfer catalysts (PTC) to replace the less active tetrabutylammonium bromide (TBAB), for the US-promoted (35 kHz, 350 W cleaning bath) Michael addition of active methylene compounds to 2-cyclohexenone (Scheme 75).[254] This fast and high-yield procedure presented the additional advantages of easy and cost effective catalyst synthesis in mild (25 °C) reaction conditions and with a simple work-up. In other studies, solvent-free sonochemical conditions were employed, in combination with commercial immobilized Novozyme lipases (*i.e.* 'Novozyme 435', 'Lipozyme TM IL' and 'Lipozyme RM IM'). In these experimental conditions, both the rate and the final yields of diacylglycerol or monoacylglycerol from vegetal oils such as soybean-oil (with a 47 kHz, 125 W, cleaning bath)[255] or olive-oil (37 kHz, 132 W, cleaning bath) were increased (in no case yield exceeded 40%).[256]

The *aza*-Michael addition reaction involving *p*-toluenesulfonamide and fumaric esters, in the presence of potassium carbonate, and under US irradiation, was also developed.[257] It has been observed that the bulkiness of the alkoxy group of fumaric esters affected significantly neither the yields, nor reaction times, since the reaction proceeded in good conditions with all linear and non-linear alkyl fumarates. The mixture was irradiated in a water ultrasonic bath at 53 °C, using an apparatus with frequency of 28 kHz and a power of 500 W. The silent test reactions, performed in the same experimental conditions, resulted in similar yields than in the sonicated reactions. As expected, the reaction times were noticeably reduced when ultrasounds were applied.

Substituted pyrazolones were prepared by Mojtahedi,[258] by bulk, catalyst-free condensation of hydrazine or phenylhydrazine with various β-ketoesters. Reactions were carried out using a high intensity US probe (24 kHz, 460 W/cm^2) as the energy source at a controlled temperature of 25 °C (Scheme 76). Initial optimization studies suggested performing reactions in solvent-free conditions. The repetition of a model reaction under conventional thermal heating (140 °C) for longer reaction times, led to unsatisfactory yields, indicating the significance of sonication for an efficient synthesis. Notably, a relatively large scale synthesis of 1-phenyl-3-propyl-1H-pyrazol-5(4H)-one was successfully performed in an excellent yield of 90% after only 25 min, using 50 mmol of reactants (instead of 5 mmol).

The same group reported the bulk, US-promoted (24 kHz, 600 W probe) formation of silyl ethers by reaction of alcohols with hexamethyldisilazane (Scheme 77). These authors observed chemoselectivity towards the less sterically hindered substrate as well as towards phenols in the presence of aromatic amines.[259]

Fused heterocycles were also prepared in a one-pot reaction of phthalhydrazide, 1,3-cyclohexanediones and aromatic aldehydes yielding the corresponding indazolophthalazinetriones. The reactions were carried out under solvent-free conditions, in the presence of (*S*)-camphorsulfonic acid ((*S*)-CSA)[260] or iodine,[261] as catalysts (Scheme 78). Comparative experiments of (*S*)-CSA catalysed reaction in silent conditions (at 80 °C) or under US irradiation (at room temperature, 200 W cleaning bath) led to very similar results in terms of yield, reaction time and selectivity. Therefore, no particular benefit other than the possibility of working at room temperature was brought by sonication. Both techniques, indeed, proved to be efficient and ecologically benign, taking into account



Scheme 77. Chemoselective alcohol protection.

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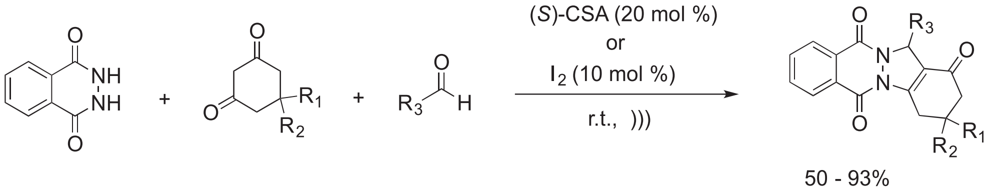
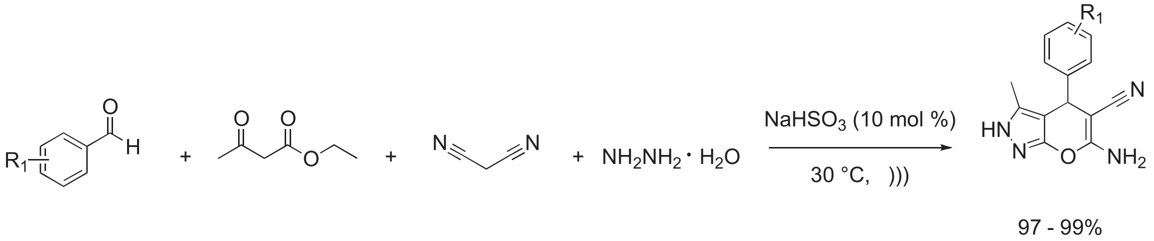


Scheme 78. Domino reaction to fused heterocycles.

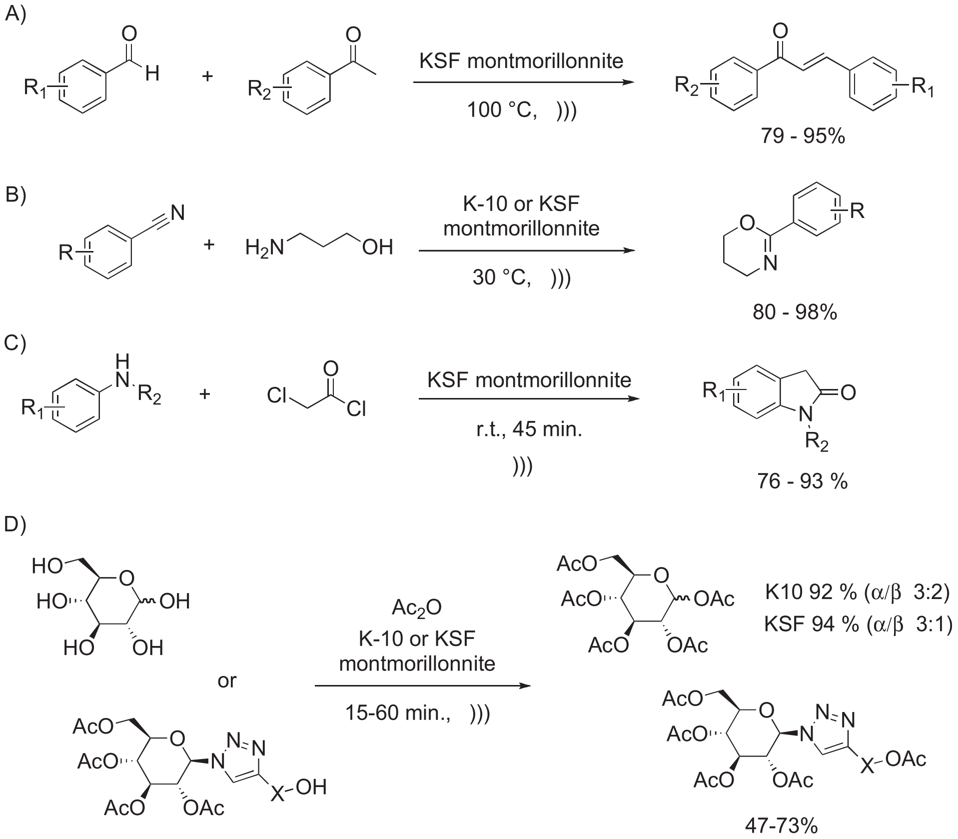


Scheme 79. Domino reaction in mild conditions.

the operational simplicity and atom-economy of the domino reaction. However, a drastic increase in yield (and kinetics) of product was observed when the reaction was catalysed by iodine (higher than 90% after 10 min sonication).[261] This was attributed to the catalyst activation, finely divided in very reactive particles by acoustic cavitation, leading to an increased in the available surface area of iodine (Scheme 78).

In a further example of multi-component domino reaction carried out under solvent-free conditions, substituted pyrano[2,3*c*] pyrazoles were obtained by sonicating of a mixture of ethyl acetoacetate, hydrazine hydrate, malonitrile and aromatic aldehydes in the presence of sodium bisulfite as catalyst, using with a 200 W cleaning bath (35 kHz) (Scheme 79).[262]

Commercially available montmorillonite clays were successfully employed in combination with sonochemical solvent-free conditions as safe and recyclable acid catalysts for organic reactions. The synthesis of *trans*-chalcones from arylmethylketones and arylaldehydes (20 kHz, 750 W US probe operating at 50% amplitude)



Scheme 80. Heterogeneous systems: Ultrasounds enhanced the reactivity of clays.

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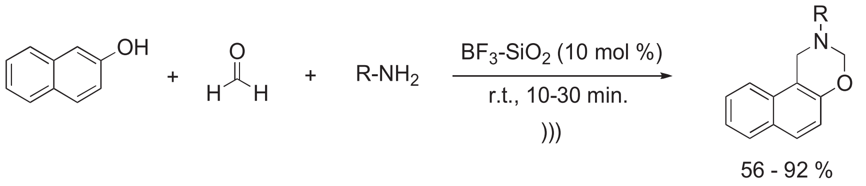
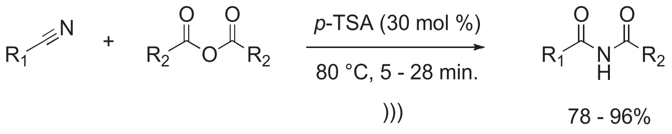


Scheme 81. Condensation reaction to 1,3-oxazines.



Scheme 82. Preparation of acyclic imides.

(Scheme 80a),[263] the conversion of arylnitriles and 3-amino-1-propanol into the corresponding oxazines[264] (24 kHz, 400 W US probe) (Scheme 80b), the preparation of oxindoles[265] (Scheme 80c) or the acetylation of sugars of natural or synthetic origin,[222] with a stereoselectivity at the anomeric carbon depending of clay used (Scheme 80d), were performed under these experimental conditions. It was normally pointed out that, in the presence of these heterogeneous systems, the improved mass transfer and the ease of structure penetration by reactants were among the most important benefits brought by the use of US-irradiation.

Supported catalysts were also used for the preparation of 1,3-oxazine derivatives. Silica-supported boron trifluoride (BF_3–SiO_2) promoted the acid-catalysed condensation reaction of aromatic (or aliphatic) heterocyclic amines with formaldehyde and 2-naphthol, under ultrasound irradiation (Scheme 81).[266] Compared to the traditional method (reflux at 80 °C for 1 h), sonication speeded up the reaction, decreasing the reaction times and increasing the yields of 1,3-oxazines, while hampering the formation of by-products, which allowed the recovery of final products without any purification.

Recently, thermal and sonochemical procedures were compared, for the *p*-TSA-catalysed synthesis of acyclic imides from anhydrides and aliphatic or aromatic nitriles, in the absence of solvent (Scheme 82).[267] The acid catalyst, although inexpensive and relatively safe, had to be used in a quite high molar ratio (30 mol %) for liquid nitriles and even higher (50 mol %) for solid nitriles. US-irradiation (35 kHz, 1000 W cleaning bath) considerably shortened the range of the reaction times from 30 to 120 min to only 5–28 min, depending on the substrates.

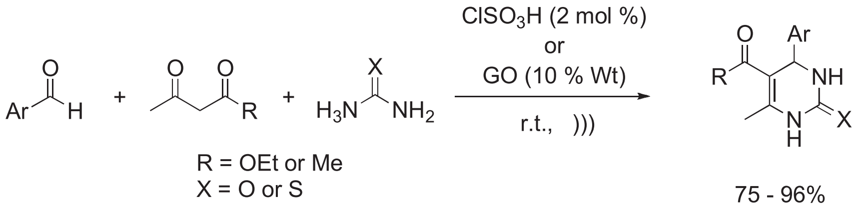
Many other solvent-free syntheses, under sonochemical conditions have been reported in the literature. Several papers describe the preparation of 3,4-dihydropyrimidin-2(1H)-ones by the Biginelli condensation of aldehydes, β-ketoesters or diketones and urea and thiourea in homogeneous[268–270] ($ClSO_3H$) or heterogeneous (Graphene Oxide, GO)[242] acid catalysed conditions (Scheme 83).

The solvent-free indium-promoted reaction of alkanoyl chlorides with several arylstannanes is a good method for the regioselective synthesis under neutral conditions of alkyl aryl ketones, in 42–84% yield (Scheme 84).[271] Reactions were carried out at 60 and 100 °C, using an ultrasonic probe (US homogenizer of 20 kHz and 375 W) equipped with a 10 mm diameter titanium horn. US apparatus was settled at 70% of output power and in a pulsed mode with different cycle. These results confirmed once again that the significant decrease in the reaction time (from 5 h at 80 °C under classical conditions to 10 min at 60 °C or 3 min at 100 °C, under irradiation) was the major advantage of ultrasound application compared to the conventional method.

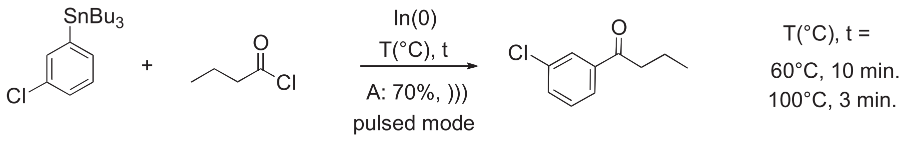
Other examples include the synthesis of pyranopyridine derivatives by the bis-iminopyridine-Fe(II)-catalysed one-pot reaction of resorcinol, malonitrile, aromatic aldehydes and cyclohexanone,[272] as well as the conversion of β-ketoesters and amines into β-enaminoesters, in the presence of catalytic amounts of acetic acid.[273]

5.2. Bulk polymerization reactions

Taking into account the efficient cavitation-induced radical formation, US-promoted radical polymerizations have already been reported several years ago[274–276] and, nowadays, are well-established procedures. An interesting study by Kojima and co-workers described the synthesis of polystyrene (PS), by sonication of the styrene liquid monomer, using two probe reactors at five different US frequencies (ranging from 23.4 kHz to 1 MHz) (Fig. 5a). They outlined a marked influence on the characteristics of the



Scheme 83. Neat Biginelli condensation.



Scheme 84. Preparation of unsymmetrical ketones.

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polymer.[277] With an acoustic frequency of 92 kHz, a maximum in PS yield was observed, while lower frequencies gave less satisfactory results, and higher frequencies produced no conversion at all. On the other hand, PS number-average molecular weight (M_n) increased from 5.5×10^4 to 11.5×10^4 g/mol lowering the frequency from 92 kHz to 23.4 kHz. As a general trend, polydispersity indexes (PDI)s tended to be higher than those of analogous PS obtained by thermal heating. According to the authors, this finding could not be explained by the coexistence of radical polymerization and degradation mechanisms under sonochemical conditions.

The same group of authors also carried out a study on the effect of sonication on the styrene autopolymerization in the presence of the nitroxide stable radical 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) at 110–135 °C.[278] The thermal polymerization under sonication proceeded similarly than a “living'' radical polymerization, to afford well-defined polystyrene. The sonication was found to both decrease the induction period, and increase the polymerization rate. The polymerization reaction was carried out inside a cylindrical Pyrex sample cell with a radius of 2 cm and a bottom thickness of 0.8 mm. A sonoreactor with a sonic probe operating at a US frequency of 27.5 kHz and with input power at the transducer of 75 W was used.

Bulk styrene polymerization was also carried out in the presence of variable amounts of MWCNTs, with the aim of obtaining a PS-based nanocomposite (PS-*g*-MWCNT) (Fig. 16) with increased electrical conductivity.[279,280] In this case, the main role of sonication was to effectively disperse the nanotubes by breaking the strong π-stacking interactions during polymerization. Nonetheless, PS could be synthesized both in the presence or in the absence of a radical initiator (AIBN), indicating how the reaction itself could easily be promoted by US irradiation. Increasing the amount of MWCNTs (up to 0.2 wt%) the PDIs of the composite augmented, due to the US-induced opening of π-bonds, followed by chain-transfer reactions and grafting of the surface with PS or AIBN itself.

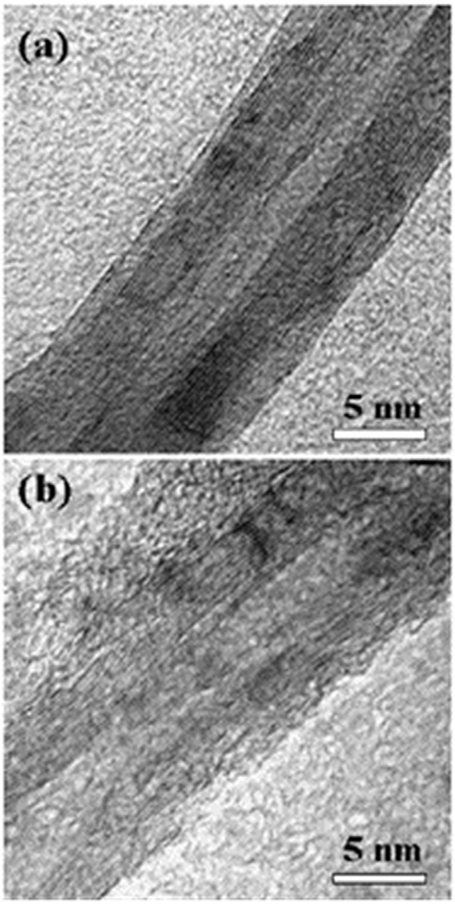

Fig. 16. TEM morphology of (a) pristine MWCNTs and (b) PS-*g*-MWCNT composite (Image reproduced from reference 261, by kind permission of Springer-Verlag).

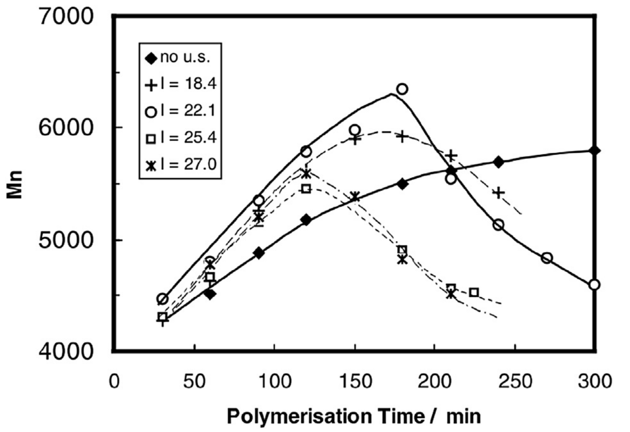

Fig. 17. The effect of US intensity *I* (indicated in W/cm^2) on the molecular weight of poly(δ-valerolactone) polymerized at 150 °C (Image reproduced from reference 263, by kind permission of Elsevier).

As already mentioned earlier in this review,[85] Cu/poly(aniline) (Fig. 5h) composites were synthesized by sonicating copper acetate monohydrate in pure aniline, using a high-intensity probe reactor, thus avoiding the re-oxidation of copper nanoparticles to Cu_2O nanocrystals, which was observed in an aniline aqueous solution. Since the efficiency of sonication strongly depends on the viscosity of the mixture, it is important to point out that the progressive increase of molecular weight during irradiation may represent a critical issue in a bulk reaction. As an example, the dibutyl tin laurate-catalysed ring opening polymerization of ε-caprolactone was moderately accelerated by the use of a probe sonicator, in the place of vigorous mechanical stirring. Nevertheless, as a M_n of around 9500 g/mol was reached after 2.5 h, the reaction could not further proceed, due to an excessive viscosity of the acoustic medium.[281] The slower silent procedure, hence, produced poly(ε-caprolactone) (PCL) (Fig. 5o) with a slightly higher M_n of about 10500 g/mol. When similar investigations were conducted with δ-valerolactone as the monomer, the formation of poly(δ-valerolactone) (Fig. 5p) was again accelerated by the use of US, but depolymerization was accordingly promoted during the late stages of the reaction and a drop in M_n was noticed after the maximum value was reached (which depends on experimental parameters) (Fig. 17).

6. Concluding remarks

Despite the large and diverse number of examples, very few data are available on comparative results obtained when direct (tip horn sonication) and indirect (cleaning bath) sonochemical procedures were applied, or when different tip horn material (pyrex, stainless steel, PEEK, etc.) were used. In addition, only few reports discuss on the role of the wave amplitude (A %) on the outcome of the reaction, and on the device used to avoid (control) temperature increase during sonication.

Undoubtedly, sonochemical conditions bring several benefits to an increasing number of organic, polymer and nanosystem syntheses. In the vast majority of cases, a strong enhancement of reaction rates is the key factor determining the appeal of US-

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promoted procedures. Indeed, reduced reaction times offer potentially interesting energy savings, compared to conventional methods based on lengthy heating and stirring. Even more importantly, the formation of pure products and the inhibition of side reactions, leads to higher yields for US activated processes, which reduce waste, and improve the economy and environmental efficiency of the process. In some cases, when conventional thermal heating and US activated processes lead to similar yields and kinetics, US-promoted reactions perform at a lower temperature, which is quite advantageous in the case of thermically unstable molecules. While somehow less emphasized, the ability of US to replace troublesome emulsifiers and phase transfer agents, is an additional asset in view of the green chemistry principles. These and many other advantages are attainable only when the sonication medium meets the requirements for effective cavitation and acoustic energy absorption processes. The low vapour pressure and volatility of solvents like water, ionic liquids, glycerol, EG or its oligomers, certainly favor their combination with sonochemical reactors. Similarly, solvent-free sonochemical conditions are rather common in the field of organic synthesis taking into account, among other convenient features, the excellent homogenization and mixing effect afforded by US irradiation. This is particularly true for heterogeneous systems or reactions involving supported catalysts. Solid surfaces are cleaned by ultrasound cavitation, and the catalytic activity enhanced. Moreover, the ease in structure penetration by reactants in the catalyst structure is possible because of improved mixing, and better mass transfer and dispersion of solids. All the surveyed publications evidence a fast-growing interest in the development of a green chemistry by coupling US as an efficient, alternative energy source, with an environmentally opportune choice of solvent.

At industrial scale, batch ultrasound reactors (with volume size ranging from 100 to 1000 L from www.etsreus.com) or continuous mode systems (with production efficiency ranging from 100 to 5000 L/h from www.hielsher.com) were already used for biomass extraction,[42] while a giant steel probe (direct sonication) was also used for diverse applications in processing and catalysis.[282] However, the major challenge for a further progress and a wider application of sonochemistry for biomaterials and pharmaceuticals includes the design of suitable equipment for large-scale applications, that are still relatively uncommon.[18]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.12.014.

References

1. Pillai UR, Sahle-Demessie E, Varma RS. *J Mater Chem*. 2002;12:3199.
2. Cintas P, Palmisano G, Cravotto G. *Ultrason Sonochem*. 2011;18:836.
3. Patel VK, Sen DJ, Patel HU, Patel CN. *J Chem Pharm Res*. 2010;2:573.
4. Cella R, Stefani HA. *Tetrahedron*. 2009;65:2619.
5. Bonrath W. *Ultrason Sonochem*. 2005;12:103.
6. Mason TJ. *Chem Soc Rev*. 1997;26:443.
7. Cintas P, Tagliapietra S, Caporaso M, Cravotto G, Tabasso S. *Ultrason Sonochem*. 2015;25:8.
8. Patil R, Bhoir P, Deshpande P, Wattamwar T, Shirude M, Chaskar P. *Ultrason Sonochem*. 2013;20:1327.
9. Paulusse JMJ, Sijbesma RP. *J Polym Sci Part A Polym Chem*. 2006;44:5445.
10. Zhang K, Park BJ, Fang FF, Choi HJ. *Molecules*. 2009;14:2095.
11. Perkas N, Gedanken A, Wehrschuetz-Sigl E, Guebitz GM, Perelshtein I, Applerot G. *Inorg Nanoparticles*. 2011:367.
12. Shchukin DG, Skorb E, Belova V, Mohwald H. *Adv Mater*. 2011;23:1922.
13. Gogate PR, Sutkar VS, Pandit AB. *Chem Eng J*. 2011;166:1066–1082.
14. Harvey G, Gachagan A, Mutasa T. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2014;61:481.
15. Pokhrel N, Vabbina PK, Pala N. *Ultrason Sonochem*. 2016;29:104.
16. Mason TJ. *Sonochemistry: The Uses of Ultrasound in Chemistry*. The Royal Society of Chemistry; 1990.
17. Frizzo CP, Bacim C, Moreira DN, et al. *Ultrason Sonochem*. 2016;32:432.
18. Gogate PR, Sutkar VS, Pandit AB. *Chem Eng J*. 2011;166:1066.
19. Plesset MS. *J Fluid Eng*. 1970;92:807.
20. A. PC, L. J-L. In: Luche J-L, ed. *Synthetic Organic Sonochemistry*. New York: Plenum Press; 1998. Ch. 2, pp. 53–56 and references therein.
21. Mason TJ. *Practical Sonochemistry. User's Guide to Applications in Chemistry and Chemical Engineering*. Chichester: Ellis Horwood; 1991:17–51.
22. Suslick KS, Hammerton DA, Cline Jr RE. *J Am Chem Soc*. 1986;108:5641.
23. Flint EB, Suslick KS. *Science*. 1991;253:1397.
24. Baig RB, Varma RS. *Chem Soc Rev*. 2012;41:1559–1584.
25. Cravotto G, Cintas P. *Chem Sci*. 2012;3:295.
26. Suslick KS. *Faraday Discuss*. 2014;170:411.
27. Bang JH, Suslick KS. *Adv Mater*. 2010;22:1039.
28. Suslick KS. *Science*. 1990;247:1439.
29. Boldyrev VV. *Ultrason Sonochem*. 1995;2:S143.
30. Cintas P, Cravotto G, Barge A, Martina K. *Top Curr Chem*. 2015;369:239.
31. Tuulmets A, Cravotto G, Salmar S, Järv J. *Mini-rev Org Chem*. 2010;7:204.
32. Ando T, Sumi S, Kawate T, Ichihara J, Hanafusa T. *J Chem Soc Chem Commun*. 1984:439.
33. Hickenboth CR, Moore JS, White SR, Sottos NR, Baudry J, Wilson SR. *Nature*. 2007;446:423.
34. Schaefer M, Icli B, Weder C, Lattuada M, Kilbinger AFM, Simon YC. *Macromolecules*. 2016;49:1630.
35. Wiggins KM, Syrett JA, Haddleton DM, Bielawski CW. *J Am Chem Soc*. 2011;133:7180.
36. Tennyson AG, Wiggins KM, Bielawski CW. *J Am Chem Soc*. 2010;132:16631.
37. Piermattei A, Karthikeyan S, Sijbesma RP. *Nat Chem*. 2009;1:133.
38. Brantley JN, Wiggins KM, Bielawski CW. *Science*. 2011;333:1606.
39. Giachi G, Frediani M, Oberhauser W, Lamaty F, Martinez J, Colacino E. *ChemSusChem*. 2014;7:919.
40. Cintas P, Barge A, Tagliapietra S, Boffa L, Cravotto G. *Nat Protoc*. 2010;5:607.
41. Veljkovic VB, Avramovic JM, Stamenkovic OS. *Renew Sustain Energy Rev*. 2012;16:1193.
42. Adam F, Abert-Vian M, Peltier G, Chemat F. *Bioresour Technol*. 2012;114:457.
43. Korkut I, Bayramoglu M. *Fuel*. 2016;180:624.
44. Hernoux A, Léveˆque J-M, Lassi U, Molina-Boisseau S, Marais M-F. *Carbohydr Polym*. 2013;92:2065.
45. Domini C, Vidal L, Cravotto G, Canals A. *Ultrason Sonochem*. 2009;16:564.
46. C. Buffa, G. Cravotto and G. Omiccioli, TO A-000766 2006.
47. Maeda M, Amemiya H. *New J Chem*. 1995;19:1023.
48. Wu Z, Borretto E, Medlock J, Bonrath W, Cravotto G. *ChemCatChem*. 2014;6:2762–2787 (and references cited therein).
49. Sacco M, Charnay C, De Angelis F, et al. *RSC Adv*. 2015;5:16878.
50. Cintas P, Mantegna S, Gaudino EC, G. C. *Ultrason Sonochem*. 2010;17:985.
51. Cravotto G, Demetri A, Nano Gian M, Palmisano G, Penoni A, Tagliapietra S. *Eur J Org Chem*. 2003:4438.
52. Zou Y, Wu H, Hu Y, et al. *Ultrason Sonochem*. 2011;18:708.
53. Shabalala NG, Pagadala R, Jonnalagadda SB. *Ultrason Sonochem*. 2015;27:423.
54. Banitaba SH, Safari J, Khalili SD. *Ultrason Sonochem*. 2013;20.
55. Jin TS, Xiao JC, Wang SJ, Li TS. *Ultrason Sonochem*. 2004;11:393.
56. Zang H, Zhang Y, Zang Y, Cheng BW. *Ultrason Sonochem*. 2010;17:495.
57. Machado P, Lima GR, Rotta M, Bonacorso HG, Zanatta N, Martins MAP. *Ultrason Sonochem*. 2011;18:293.
58. Jin TS, Zhang JS, Wang AQ, Li TS. *Ultrason Sonochem*. 2006;13:220.
59. Rostamizadeh S, Amani AM, Mahdavinia GH, Amiri G, Sepehrian H. *Ultrason Sonochem*. 2010;17:306.
60. Arcadi A, Alfonsi M, Marinelli F. *Tetrahedron Lett*. 2009;50:2060.
61. Rogozinska-Szymczak M, Adamkiewicz A, Mlynarski J. *Green Chem*. 2011;13:1155.
62. Rogozinska-Szymczak M, Mlynarski J. *Tetrahedron Asymmetry*. 2014;25:813.
63. Martins MAP, Pereira CMP, Cunico W, et al. *Ultrason Sonochem*. 2006;13:364.
64. Li JT, Sun MX, He GY, Xu XY. *Ultrason Sonochem*. 2011;18:412.
65. Joshi RS, Mandhane PG, Diwakar SD, Gill CH. *Ultrason Sonochem*. 2010;17:298.
66. Pagadala R, Maddila S, Jonnalagadda SB. *Ultrason Sonochem*. 2014;21:472.
67. Sweety S, Jomy KJ, Suman LJ, Bir S. *Green Chem Lett Rev*. 2010;3:23.
68. Ziarati A, Safaei-Ghomi J, Rohani S. *Ultrason Sonochem*. 2013;20:1069.
69. Ramazani A, Rouhani M, Joo SW. *Ultrason Sonochem*. 2016;28:393.
70. Kamble S, Kumbhar A, Rashinkar G, Barge M, Salunkhe R. *Ultrason Sonochem*. 2012;19:812.
71. Ozturkcan SA, Turhan K, Turgut Z. *Chem Pap*. 2012;66:61.
72. Azizi N, Davoudpour A, Eskandari F, Batebi E. *Monatsh Chem*. 2013;144:405.
73. Azizi N, Gholibeglo E, Maryami M, Nayeri SD, Bolourtchian SM. *C R Chim*. 2013;16:412.
74. Varma RS, Naicker KP, Kumar D. *J Mol Catal A Chem*. 1999;149:153.

75. Rup S, Sindt M, Oget N. *Tetrahedron Lett*. 2010;51:3123.
76. An G, Ji X, Han J, Pan Y. *Synth Commun*. 2011;41:1464.
77. Eftekhari-Sis B, Vahdati-Khajeh S. *Curr Chem Lett*. 2013;2:85.
78. Almeida QAR, Faria RB. *Green Chem Lett Rev*. 2013;6:129.
79. Biggs S, Grieser F. *Macromolecules*. 1995;28:4877.
80. Fujiwara H, Ishida T, Taniguchi N, Wada S. *Polym Bull*. 1999;42:197.
81. Xia H, Wang Q, Liao Y, et al. *Ultrason Sonochem*. 2002;9:151.
82. Yan L, Wu H, Zhu Q. *Green Chem*. 2004;6:99.
83. Yin N, Chen K, Kang W. *Ultrason Sonochem*. 2006;13:345.
84. Teo BM, Ashokkumar M, Grieser F. *Phys Chem Chem Phys*. 2011;13:4095.
85. Vijaya Kumar R, Mastai Y, Diamant Y, Gedanken A. *J Mater. Chem*. 2001;11:1209.
86. Jing X, Wang Y, Wu D, Qiang J. *Ultrason Sonochem*. 2007;14:75.
87. de Barros RA, de Azevedo WM. *Synth Met*. 2010;160:1387.
88. Kowsari E, Faraghi G. *Ultrason Sonochem*. 2010;17:718.
89. Sahoo S, Battacharya P, Hatui G, Ghosh D, Kumar Das C. *J Appl Polym Sci*. 2013;128:1476.
90. Bhanvase BA, Darda NS, Veerkar NC, Shende AS, Satpute SR, Sonawane SH. *Ultrason Sonochem*. 2015;24:87.
91. Pomposo J-A, Ochoteco E, Pozo C, Carrasco P-M, Grande H-J, Rodriguez F-J. *Polym Adv Technol*. 2006;17:26.
92. Prasad K, Sonawane S, Zhou M, Ashokkumar M. *Chem Eng J*. 2013;219:254.
93. Hasanzadeh I, Barikani M, Mahdavian AR. *Polym Eng Sci*. 2016;56:214.
94. Chowdhury P, Saha SK, Guha A, Saha SK. *Appl Surf Sci*. 2012;261:598.
95. Panigrahi R, Srivastava SK. *RSC Adv*. 2013;3:7808.
96. Kashin AS, Ananikov VP. *J Org Chem*. 2013;78:11117.
97. Li C, Cai W, Kan C, Fu G, Zhang L. *Mater. Lett*. 2003;58:196.
98. Cubillana-Aguilera LM, Franco-Romano M, Gil ML, Naranjo-Rodriguez I, de Cisneros JL, Palacios-Santander JM. *Ultrason Sonochem*. 2011;18:789.
99. Franco-Romano M, Gil MLA, Palacios-Santander JM, et al. *Ultrason Sonochem*. 2014;21:1570.
100. Gao T, Wang T. *Green Chem*. 2004;6:2558.
101. Dang F, Enomoto N, Hojo J, Enpuku K. *Ultrason Sonochem*. 2009;16:649.
102. Marchegiani G, Imperatori P, Mari A, et al. *Ultrason Sonochem*. 2012;19:877.
103. Morel A-L, Nikitenko SI, Gionnet K, et al. *ACS Nano*. 2008;2:847.
104. Mandel K, Kolb C, Straßer M, Dembski S, Sextl G. *Colloid Surf A*. 2014;457:27.
105. Zhao D, Li M, Zhang D, Baig SA, Xu X. *Ultrason Sonochem*. 2013;20:864.
106. Zhao D, Zheng Y, Li M, Baig SA, Wu D, Xu X. *Ultrason Sonochem*. 2014;21:1714.
107. Ban I, Kristl M, Danc V, Danc A, Drofenik M. *Mater. Lett*. 2012;67:56.
108. Goharshadi EK, Sajjadi SH, Mehrkhah R, Nancarrow P. *Chem Eng J*. 2012;209:113.
109. Fu L-H, Dong Y-Y, Ma M-G, Yue W, Sun S-L, Sun R-C. *Ultrason Sonochem*. 2013;20:1188.
110. Dang F, Kato K, Imai H, Wada S, Haneda H, Kuwabara M. *Chem Eng J*. 2011;170:333.
111. Zhao Y, Liao X-H, Hong J-M, Zhu J-J. *Mater. Chem Phys*. 2004;87:149.
112. Dharmarathna S, King'ondu CK, Pedrick W, Pahalagedara L, Suib SL. *Chem Mater*. 2012;24:705.
113. Raj BGS, Asiri AM, Qusti AH, Wu JJ, Anandan S. *Ultrason Sonochem*. 2014;21:1933.
114. Abbas M, Torati SR, Rao BP, Abdel-Hamed MO, Kim CG. *J Alloy Compd*. 2015;644:774.
115. Kianpour G, Salavati-Niasari M, Emadi H. *Ultrason Sonochem*. 2013;20:418.
116. Mohandes F, Salavati-Niasari M. *Ultrason Sonochem*. 2013;20:354.
117. Lin H-t, Li H-l, Chen X-y, Yang M, Qi Y-x. *Fenzi Cuihua*. 2010;24:99.
118. Banerjee P, Chakrabarti S, Maitra S, Dutta BK. *Ultrason Sonochem*. 2012;19:85.
119. Morsella M, Giammatteo M, Arrizza L, Tonucci L, Bressan M, d'Alessandro N. *RSC Adv*. 2015;5:57453.
120. Jhuang YY, Cheng WT. *Ultrason Sonochem*. 2016;28:327.
121. Chang X, Sun S, Yin Y. *Mater. Chem Phys*. 2011;126:717.
122. Angı A, Sanlı D, Erkey C, Birer Ö. *Ultrason Sonochem*. 2014;21:854.
123. He C, Liu L, Fang Z, Li J, Guo J, Wei J. *Ultrason Sonochem*. 2014;21:542.
124. Soofivand F, Salavati-Niasari M, Mohandes F. *J Ind Eng Chem*. 2014;20:3780.
125. Sanoop PK, Mahesh KV, Nampoothiri KM, Mangalaraja RV, Ananthakumar S. *J Appl Polym Sci*. 2012;126:E233.
126. Kowsari E. *J Nanopart Res*. 2011;13:3363.
127. Yadav RS, Mishra P, Pandey AC. *Ultrason Sonochem*. 2008;15:863.
128. Zak AK, Majid WH, Wang HZ, Yousefi R, Golsheikh AM, Ren ZF. *Ultrason Sonochem*. 2013;20:395.
129. Khanjani S, Morsali A, Joo SW. *Ultrason Sonochem*. 2013;20:734.
130. Li X, Li Y, Li S, et al. *Cryst Growth Des*. 2005;5:911.
131. Zhang H, Yang D, Ma X. *Mater. Lett*. 2008;63:1.
132. Vijaya Kumar R, Koltypin Y, Cohen YS, et al. *J Mater. Chem*. 2000;10:1125.
133. Vijaya Kumar R, Elgamiel L, Diamant Y, Gedanken A. *Langmuir*. 2000;17:1406.
134. Vijaya Kumar R, Diamant Y, Gedanken A. *Chem Mater*. 2000;12:2301.
135. Huang B, He Q, Fa W, Li P, Zhang Y, Zheng Z. *Mater. Res Bull*. 2012;47:2599.
136. Pereiro AB, Araújo JMM, Esperança JMSS, Marrucho IM, Rebelo LPN. *J Chem Thermodyn*. 2012;46:2.
137. Moniruzzaman M, Nakashima K, Kamiya N, Goto M. *Biochem Eng J*. 2010;48:295.
138. Welton T. *Coord Chem Rev*. 2004;248:2459.
139. Matic A, Scrosati B. *MRS Bull*. 2013;38:533.
140. Oxley JD, Prozorov T, Suslick KS. *J Am Chem Soc*. 2003;125:11138.
141. Dupont J, Spencer J. *Angew Chem Int Ed*. 2004;43:5296.
142. Swatloski RP, Holbrey JD, Rogers RD. *Green Chem*. 2003;5:361.
143. Arduengo III AJ. *Acc Chem Res*. 1999;32:913.
144. Chatel G, Pflieger R, Naffrechoux E, et al. *ACS Sustain Chem Eng*. 2013;1:137.
145. Gholap AR, Venkatesan K, Daniel T, Lahoti RJ, Srinivasan KV. *Green Chem*. 2003;5:693.
146. Gholap AR, Venkatesan K, Daniel T, Lahoti RJ, Srinivasan KV. *Green Chem*. 2004;6:147.
147. Venkatesan K, Pujari SS, Lahoti RJ, Srinivasan KV. *Ultrason Sonochem*. 2008;15:548.
148. Zhao S, Wang X, Zhang L. *RSC Adv*. 2013;3:11691.
149. Naeimi H, Nazifi ZS. *J Ind Eng Chem Res*. 2014;20:1043.
150. Sandhu S, Sandhu JS. *Org Med Chem Lett*. 2013;3:2.
151. Zakeri M, Nasef MM, Abouzari-Lotf E. *J Mol Liq*. 2014;199:267.
152. Bravo JL, Lopez I, Cintas P, Silvero G, Arevalo MJ. *Ultrason Sonochem*. 2006;13:408.
153. Noei J, Khosropour AR. *Ultrason Sonochem*. 2009;16:711.
154. Villagran C, Banks CE, Pitner WR, Hardacre C, Compton RG. *Ultrason Sonochem*. 2005;12:423.
155. Heravi MR. *Ultrason Sonochem*. 2009;16:361.
156. Heravi MR. *J Univ Chem Technol Metall*. 2009;44:86.
157. Rostami M, Khosropour AR, Mirkhani M, Mohammadpoor-Baltork I, Moghadam M, Tangestaninejad S. *C R Chim*. 2011;14:869.
158. Reddy MV, Reddy AVS, Jeong YT. *Res Chem Int*. 2016;42:4893.
159. Borikar SP, Daniel T. *Ultrason Sonochem*. 2011;18:928.
160. Li X, Lin Q, Ma L. *Ultrason Sonochem*. 2010;17:752.
161. Pawar OB, Chavan FR, Sakate SS, Shinde ND. *Chin J Chem*. 2010;28:69.
162. Yadav N, Hussain MK, Ansari MI, Gupta PK, Hajela K. *RSC Adv*. 2013;3:540.
163. Zlotin SG, Bogolyubov AV, Kryshtal GV, Zhdankina GM, Struchkova MI, Tartakovsky VA. *Synthesis*. 2006:3849.
164. Li B, Ge C, Ying AG. *Adv Mater. Res*. 2012;531:428.
165. Li D, Zang H, Wu C, Yu NQ. *Ultrason Sonochem*. 2013;20:1144.
166. Narayanaperumal S, da Silva RC, Feu KS, de la Torre AF, Corrêa AG, Paixão MW. *Ultrason Sonochem*. 2013;20:793.
167. Qian H, Wang Y, Liu D. *Ind Eng Chem Res*. 2013;52:13272.
168. Palakshi Reddy B, Rajesh K, Vijayakumar V. *Arab J Chem*. 2015;8:138.
169. He JY, Jia HZ, Yao QG, et al. *Ultrason Sonochem*. 2015;22:144.
170. Li BL, Zhong AG, Ying AG. *J Heterocycl Chem*. 2015;52:445.
171. Zang H, Su Q, Mo Y, Cheng BW, Jun S. *Ultrason Sonochem*. 2010;17:749.
172. Zang H, Wang M, Cheng BW, Song J. *Ultrason Sonochem*. 2009;16:301.
173. Deshmukh RR, Rajagopal R, Srinivasan KV. *Chem Commun*. 2001:1544.
174. Rajagopal R, Jarikote DV, Srinivasan KV. *Chem Commun*. 2002:616.
175. Harjani JR, Abraham TJ, Gomez AT, Garcia MT, Singer RD, Scammells PJ. *Green Chem*. 2010;12:650.
176. Chatel G, Goux-Henry C, Kardos N, Suptil J, Andrioletti B, Draye M. *Ultrason Sonochem*. 2012;19:390.
177. Matuszek K, Zawadzki P, Czardybonb W, Chrobok A. *New J Chem*. 2014;38:237.
178. Heravi MRP, Fakhr F. *Tetrahedron Lett*. 2011;52:6779.
179. Lee SH, Nguyen HM, Koo Y-M, Ha SH. *Proc Biochem*. 2008;43:1009.
180. Wang J, Wang S, Li Z, Gu S, Wu X, Wu F. *J Mol Catal B Enzym*. 2015;111:21.
181. Jin Y, Wang P, Yin D, et al. *Colloids Surf A Physicochem Eng Asp*. 2007;302:366.
182. Zhang S, Zhang Y, Wang Y, Liu S, Deng Y. *Phys Chem Chem Phys*. 2012;14:5132.
183. Goharshadi EK, Ding Y, Jorabchi MN, Nancarrow P. *Ultrason Sonochem*. 2009;16:120.
184. Alammar T, Mudring A-V. *ChemSusChem*. 2011;4:1796.
185. Rabieh S, Bagheri M. *Mater. Lett*. 2014;122:190.
186. Sabbaghan M, Beheshtian J, Mirsaeidi SAM. *Ceram Int*. 2014;40:7769.
187. Gao B, Yang YT, Yang H, Zhang SY, Liu XJ. *Sci China Phys Mech Astron*. 2013;56:1280.
188. Alammar T, Noei H, Wang Y, Mudring AV. *Nanoscale*. 2013;5:8045.
189. de la Parra-Arciniega SM, García-Gómez NA, Garcia-Gutierrez DI, Salinas-Estevané P, Sánchez EM. *Mat Sci Semicon Proc*. 2014;23:7.
190. Zhuravlev OE, Presnyakov IA, Voronchikhina LI. *Russ J Appl Chem*. 2015;88:914.
191. Park HS, Choi BG, Yang SH, et al. *Small*. 2009;5:1754.
192. Park HS. *Hwahak Konghak*. 2012;50:729.
193. Jacob DS, Kahlenberg V, Wurst K, et al. *Eur J Inorg Chem*. 2005;2005:522.
194. Jacob DS, Makhluf S, Brukental I, et al. *Eur J Inorg Chem*. 2005;2005:2669.
195. Totten GE, Clinton NA, Matlock J. *J Macromol Sci Rev Macromol Chem Phys*. 1998;38:77.
196. Colacino E, Martinez J, Lamaty F, et al. *Coord Chem Rev*. 2012;256:2893.
197. Chen J, Spear SK, Huddleston JG, Rogers RD. *Green Chem*. 2005;7:64.
198. Silva AdC, de Souza ALF, Antunes OAC. *J Organomet Chem*. 2007;692:3104.
199. Madan Y, Gupta R, Menghani E. *Int J Res Chem Environ*. 2015:106.
200. Rao MS, Haritha M, Chandrasekhar N, Mandava V, Rao B, Pal M. *Tetrahedron Lett*. 2014;55:1670.
201. Cravotto G, Cintas P. *Angew Chem Int Ed Engl*. 2007;46:5476.
202. Azua A, Mata JA, Heymes P, et al. *Adv Synth Catal*. 2013:1107.
203. Azua A, Mata JA, Peris E, Lamaty F, Martinez J, Colacino E. *Organometallics*. 2012;31:3911.
204. Lianga C, Tangb Z, Qiana W, Shia C, Songa H. *J Chem Pharm Res*. 2014;6:798.
205. Khan M, Karamthulla NS, Choudhury LH, Faizi MSH. *RSC Adv*. 2015;5:22168.
206. Nemati F, Hasan S, Elhampour NA. *Chin Chem Lett*. 2015;26:1397.
207. He J, Shi L, Liu S, Jia P, Wang J, Hu R. *Monatsh Chem*. 2014;145:213.
208. Mesquita PRR, Almeida JS, Teixeira LSG, da SAF, Silva LA. *J Braz Chem Soc*. 2013;24:280.

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209. T. R. Bastami and M. H. Entezari, Mater. Res Bull 48, 3149.
210. Qiu L, Pol VG, Wei Y, Gedanken A. *New J Chem*. 2004;28:1056.
211. Nemamcha A, Moumeni H, Rehspringer JL. *Phys Procedia*. 2009;2:713.
212. Matin MA, Jang JH, Kwon YU. *J Power Sources*. 2014;262:356.
213. Abu-Much R, Gedanken A. *Chem Eur J*. 2008;14:10115.
214. Ding T, Zhang J-R, Hong J-M, Zhu J-J, Chen H-Y. *J Cryst Growth*. 2004;260:527.
215. Phuruangrat A, Thongtem T, Thongtem S. *Chalcogenide Lett*. 2011;8:291.
216. Cravotto G, Orio L, Calcio Gaudino E, Martina K, Tavor D, Wolfson A. *ChemSusChem*. 2011;4:1130.
217. Hamel A, Sacco M, Mnasri N, et al. *ACS Sustain Chem Eng*. 2014;2:1353.
218. Mendes SR, Thurow S, Penteado F, et al. *Green Chem*. 2015;17:4334.
219. Bhosale MA, Bhanage BM. *Adv Powder Tech*. 2016;27:238.
220. Cenci SM, Cox LR, Leeke GA. *ACS Sustain Chem Eng*. 2014;2:1280.
221. Cargnelutti R, Lang ES, Schumacher RF. *Tetrahedron Lett*. 2015;56:5218.
222. De Oliveira RN, Xavier AdL, Guimarães BM, et al. *J Chil Chem Soc*. 2014;59:2610.
223. Singh BS, Lobo HR, Pinjari DV, Jarag KJ, Pandit AB, Shankarling GS. *Ultrason Sonochem*. 2013;20:287.
224. Yadav UN, Shankarling GS. *J Mol Liq*. 2014;195:188.
225. Koltypin Y, Perkas N, Gedanken A. *J Mater. Chem*. 2004;14:2975.
226. Kuijpers MWA, van Eck D, Kemmere MF, Keurentjes JTF. *Science*. 2002;298:1969.
227. Andrews PC, Peatt AC, Raston CL. *Tetrahedron Lett*. 2002;43:7541.
228. Lopez-Pestana JM, Avila-Rey MJ, Martin-Aranda RM. *Green Chem*. 2002;4:628.
229. Calvino-Casilda V, Lopez-Peinado AJ, Martin-Aranda RM, Ferrera-Escudero S, Duran-Valle CJ. *Carbon*. 2004;42:1363.
230. Calvino-Casilda V, Martin-Aranda RM, Lau WN, Zhang XF, Yeung KL. *Stud Surf Sci Cat*. 2005;158:1985.
231. Perozo-Rondón E, Martín-Aranda RM, Casal B, et al. *Catal Today*. 2006;114:183.
232. Calvino V, Picallo M, López-Peinado AJ, Martín-Aranda RM, Durán-Valle CJ. *Appl Surf Sci*. 2006;252:6071.
233. Gutierrez-Sanchez C, Calvino-Casilda V, Perez-Mayoral E, et al. *Catal Lett*. 2009;128:318.
234. Puri S, Kaur B, Parmar A, Kumar H. *Ultrason Sonochem*. 2009;16:705.
235. Puri S, Kaur B, Parmar A, Kumar H. *Org Prep Proced Int*. 2012;44:91.
236. Prousis KC, Avlonitis N, Heropoulos GA, Calogeropoulou T. *Ultrason Sonochem*. 2014;21:937.
237. Khaligh NG. *Ultrason Sonochem*. 2013;20:1062.
238. Martin-Aranda RM, Ortega-Cantero E, Rojas-Cervantes ML, Vicente-Rodriguez MA, Banares-Munoz MA. *J Chem Technol Biotechnol*. 2005;80:234.
239. Liu Q, Ai H, Li Z. *Ultrason Sonochem*. 2011;18:477.
240. Zhang L-J, Xia J, Zhou Y-Q, Wang H, Wang S-W. *Synth Commun*. 2012;42:328.
241. Xia M, Lu YD. *Ultrason Sonochem*. 2007;14:235.
242. Bhattacharya T, Majumdar B, Dey D, Sarma TK. *RSC Adv*. 2014;4:45831.
243. Dar B, Singh A, Sahu A, et al. *Tetrahedron Lett*. 2012;53:5497.
244. Niralwad KS, Shingate BB, Shingare MS. *Ultrason Sonochem*. 2010;17:760.
245. Sonar SS, Sadaphal SA, Labade VB, Shingate BB, Shingare MS. *Phosphorus, Sulfur, Silicon, Relat Elem*. 2010;185:65.
246. Bouzina A, Nour-eddine A, Berredjem M. *Res Chem Int*. 2016;42:5993.
247. Mandhane PG, Joshi RS, Nagargoje DR, Gill CH. *Tetrahedron Lett*. 2010;51:1490.
248. Belhani B, Berredjem M, Le Borgne M, Bouaziz Z, Lebreton J, Nour-Eddine A. *RSC Adv*. 2015;5:39324.
249. Dar BA, Pandey N, Singh S, et al. *Tetrahedron Lett*. 2014;55:623.
250. Bouzina A, Belhani B, Nour-Eddine A, Berredjem M. *RSC Adv*. 2015;5:46272.
251. Dar BA, Ahmad SN, Wagay MA, et al. *Tetrahedron Lett*. 2013;54:4880.
252. Cui C, Zhu C, Du X-J, Wang Z-P, Li Z-M, Zhao W-G. *Green Chem*. 2012;14:3157.
253. Namboodiri VV, Varma RS. *Org Lett*. 2002;4:3161.
254. Oge A, Mavis ME, Yolacan C, Aydogan F. *Turk J Chem*. 2012;36:137.
255. Babicz I, Leite SG, de Souza RO, Antunes OA. *Ultrason Sonochem*. 2010;17:4.
256. Fiametti KG, Sychoski MM, De Cesaro A, et al. *Ultrason Sonochem*. 2011;18:981.
257. Imanzadeh G, Kazemi F, Zamanloo M, Mansoori Y. *Ultrason Sonochem*. 2013;20:722.
258. Mojtahedi MM, Javadpour M, Abaee MS. *Ultrason Sonochem*. 2008;15:828.
259. Mojtahedi MM, Saeed Abaee M, Hamidi V, Zolfaghari A. *Ultrason Sonochem*. 2007;14:596.
260. Shukla G, Verma RK, Verma GK, Singh MS. *Tetrahedron Lett*. 2011;52:7195.
261. Varghese A, Nizam A, Kulkarni R, George L. *Eur J Org Chem*. 2013;4:132.
262. Darandale SN, Sangshetti JN, Shinde DB. *J Korean Chem Soc*. 2012;56:328.
263. Chtourou M, Abdelhedi R, Frikha MH, Trabelsi M. *Ultrason Sonochem*. 2010;17:246.
264. Mohammadpoor-Baltork I, Moghadam M, Tangestaninejad S, Mirkhani V, Eskandari Z. *Ultrason Sonochem*. 2010;17:857.
265. Dandia A, Bhati DS, Jain AK, Sharma GN. *Ultrason Sonochem*. 2011;18:1143.
266. Reddy MV, Lim KT, Kim JT, Jeong YT. *J Chem Res*. 2012:398.
267. Nasr-Esfahani M, Montazerozohori M, Filvan N. *J Serb Chem Soc*. 2012;77:415.
268. Singh K, Singh S, Kaur P. *Lett Org Chem*. 2006;3:201.
269. Chabukswar VV, Handore KN, Bhavsar SV, et al. *J Macromol Sci Part A Pure Appl Chem*. 2013;50:411.
270. Al-Kadasi AMA, Nazeruddin GM. *J Chem Pharm Res*. 2010;2:536.
271. Lo Fiego MJ, Badajoz MA, Domini C, Chopa AB, Lockhart MT. *Ultrason Sonochem*. 2013;20:826.
272. Damavandi S, Sandaroos R. *J Chem Sci*. 2012;124:483.
273. Brandt CA, da Silva ACMP, Pancote CG, Brito CL, da Silveira MAB. *Synthesis*. 2004;10:1557.
274. Kruus P, Patraboy TJ. *J Phis Chem*. 1985;89:3379.
275. Price GJ, Daw MR, Newcombe NJ, Smith PF. *Brit Polym J*. 1990;23:63.
276. Koda S, Suzuki A, Nomura H. *Polym J*. 1995;27:1144.
277. Kojima Y, Koda S, Hiroyasu N. *Ultrason Sonochem*. 2001;8:75.
278. Kojima Y, Koda S, Nomura H, Kawaguchi S. *Ultrason Sonochem*. 2001;8:81.
279. Kim ST, Choi HJ, Hong SM. *Colloid Polym Sci*. 2007;285:593.
280. Choi HJ, Zhang K, Lim JY. *J Nanosci Nanotechnol*. 2007;7:3400.
281. Price GJ, Lenz EJ, Ansell CWG. *Eur Polym J*. 2002;38:1753.
282. Russell JP, Smith M. In: Mason TJ, ed. *Advances in Sonochemistry*. vol. 5. London: JAI Press; 1999:279–302.

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