

Ionic Liquid and Microwave-Assisted Organic Synthesis: A “Green” and Synergic Couple

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Abstract: In the present century an ever-growing number of papers have been published describing the use of ionic liquids (ILs) on Microwave-Assisted Organic Synthesis (MAOS). In general, these works have shown evident advantages of this couple (IL/MAOS) respect to the conventional synthetic procedures for the generation of fast, efficient and environmental friendly synthetic methodologies. This review focuses on the advances in the developing of innovative applications of ILs/MAOS.

Key words: ionic liquids, microwave, organic synthesis.

Resumen: En el presente siglo se están publicando un número creciente de artículos relacionados con la aplicación de los líquidos iónicos (LIs) a la síntesis orgánica asistida por microondas. En general, estos trabajos muestran evidentes ventajas de la aplicación de esta dupla (LI/SOAM) respecto a los métodos convencionales de síntesis en la generación de procedimientos sintéticos rápidos, eficientes y amigables al ambiente. El presente trabajo revisa los avances en las aplicaciones novedosas de la tecnología IL/SOAM.

Palabras clave: Líquidos iónicos, microondas, síntesis orgánica.

Introduction

Microwave-assisted organic synthesis (MAOS) has been known since 1986 [1]. This “non-conventional” synthetic method has shown broad applications as a very efficient way to accelerate the course of many organic reactions, producing high yields and higher selectivity, lower quantities of side products and, consequently, easier work-up and purification of the products. MAOS is considered as an “green” technology, principally since many organic reactions can be carry out in solvent-free conditions [2].

Therefore, the growing interest in academic, research and industrial laboratories is not surprising and is reflected in an exponential increase in the productivity of scientific papers, books [3], and reviews [4] related to the use of this technology.

In recent years, researchers have applied microwave as a tool in order to diminish reaction time, avoid side products, increase yield and simplify the course of reactions for combinatorial chemistry [5].

Ionic liquids (ILs) has attracted the attention on scientific community in the last decade, due their particular properties [6] and their applications in Organic Synthesis [7], catalysis [8], biocatalysis [9], liquid-liquid separations [10], extraction [11] and dissolution (celulose in microwave [12] and petroleum asphaltenes in microwave [13]) processes, nanomaterials synthesis [14], polymerization reactions [15] and electrochemistry [16]. ILs are an excellent alternative to substitute volatile organic solvents in more environmental friendly technologies (“green technologies”), since their very low vapor pressures, their thermal and chemical stability, their ability to act as catalyst, and their non-flammability and non-corrosives properties.

Recent trends in MAOS use ILs as solvent, co-solvent and/or catalyst, since they are “ecofriend solvents” [17] and since their ionic nature, allows a very effective coupling

with microwave energy [18]. MAOS has also been widely employed to synthesized ILs.

The synergies arising from the combined use of MW and ILs will certainly go a long way to meet the increasing demand for environmentally benign chemical processes [19].

Herein, we review the papers about the applications of MAOS of ILs and the applications of ILs for improving MAOS.

What microwave are?

A microwave (MW) is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum (300-300000 MHz). Microwave heating (dielectric heating) is a very efficient process due to the microwave couple directly with the molecules that are present in the reaction mixture, leading to a fast rise in temperature, faster reactions and cleaner chemistry.

The two fundamental mechanisms for transferring energy from microwaves to the substance are dipole rotation and ionic conduction.

Dipole rotation is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave.

Ionic conduction mechanism consists in the instantaneous superheating of the ionic substance due to the ionic motion generated by the electric field. When the temperature increases, the transfer of energy becomes more efficient. Since their ionic character, ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction.

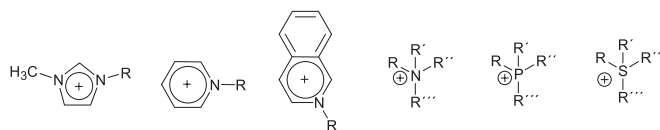
The MW theory and how the MW increase reactions rate has been recently discussed in details by several authors [3,4].

The increased interest in microwave technology has raised the number of companies supporting new microwave ovens for laboratory use [20], such as mono-mode microwave, also called single-mode microwave [21].

Ionic liquids (ILs). Properties and applications

ILs are ionic compounds in which, at least the cation is an organic type cation. ILs contain only ionic species and sometimes are known as molten salt, however while a molten salt is generally thought to refer to a high-melting, highly viscous and very corrosive medium, ionic liquids are already liquid at low temperatures ($< 100^{\circ}\text{C}$) and have relatively low viscosity. The apparently somewhat arbitrary line drawn between molten salts and ILs at a melt temperature of 100°C can be justified by the abrupt improvement in the range of applications for liquid salts below this temperature. Even though some examples are known in which high-temperature salt melts have been successfully used as reaction media for synthetic applications, only a liquid range below 100°C can enable the versatile substitution of conventional, organic solvents by ionic liquid [22].

The most important, reported cation types in the ILs are shown below.



Anions can be organic or inorganic and the combinations of the different cations and anions can dramatically change the physicochemical properties of the IL generated [23]. The most typical anions are: Cl⁻, Br⁻, [BF₄]⁻, [PF₆]⁻, [SbF₆]⁻, [AlCl₄]⁻, [AuCl₄]⁻, [NO₃]⁻, [NO₂]⁻, [SO₄]⁻, [AcO]⁻, Tf⁻, [N(OTf)₂]⁻, [CF₃CO₂]⁻, [CF₃SO₃]⁻, [PhCOO]⁻, [C(CN)₂]⁻, [RSO₄]⁻, [OTs]⁻, [SCN]⁻.

The main properties of ILs for their applications in MAOS are the following:

Extremely low vapor pressure. To a difference of the classical organic solvents, ILs are known to have a negligible vapor pressure below their decomposition temperature. This is the main reason because ILs are considered environmental friendly solvents.

Thermal Stability: The thermal stability of ILs is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds, respectively. The nature of the ILs, containing organic cations, restricts upper stability temperatures, pyrolysis generally occurs between $350\text{--}450^{\circ}\text{C}$, if no other lower temperature decomposition pathways are accessible. In most cases, decomposition occurs with complete mass loss and volatilization of the component fragments.

Solubility: Many ionic ILs possess the ability to dissolve a wide range of inorganic and organic compounds. This is important for dissolving disparate combinations of reagents into the same phase.

ILs are considered to be polar solvents, but can be non-coordinating (mainly depending on the ionic liquid anions). The polarity of many ILs is intermediate between water and chlorinated organic solvents and varies, depending on the nature of the ionic liquid components.

Several processes would be impossible with conventional solvents because of their limited liquid range or miscibility. Even greater potential is the use of ILs for chemical synthesis because the charged nature of these solvents can influence the synthesis itself.

Electrochemical Stability. ILs often have wide electrochemical potential windows, they have reasonably good electrical conductivity. The electrochemical window of an ionic liquid is influenced by the stability of the cation against electrochemical reduction-processes and the stability of the anion against oxidation-processes.

Non-flammability. ILs are safe for handling.

Catalytic properties. The catalytic properties in organic and inorganic synthesis have been widely described [24]. Also biocatalytic transformations in ILs have been performed using a range of different enzymes and some whole cell preparations, mainly in biphasic aqueous systems using hydrophobic dialkylimidazolium ILs [25].

At the present, ILs are employed in different industrial processes [26] and several ILs are commercially available at relatively high cost [27].

Microwave-assisted ILs synthesis

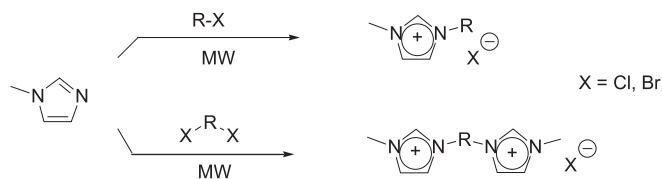
The first step in the synthesis of ILs is the quaternization of a nitrogen containing heterocycle, such as 1-substituted imidazole, pyridine or isoquinoline, amine, mercaptants or phosphane to form the cation. In a second step, the halogen ions is interchanged for the desired anions, it must be ensured that no halide ions remain in the system.

Employing conventional synthetic methods, ILs synthesis in refluxing solvent required several hours (8–72 h) at relatively high temperature, depend on the reactivity of the alkylation reagent, to afford reasonable yield and employing a large excess of alkyl halides and organic solvent at the reaction medium.

The application of microwave on ILs synthesis improved dramatically the time required to obtain these compounds as is showed below.

In 2001, Varma et al. described for the first time the synthesis of ILs under microwave irradiation conditions. In this paper, 1-alkyl-3-methylimidazolium halides (Cl and Br) were

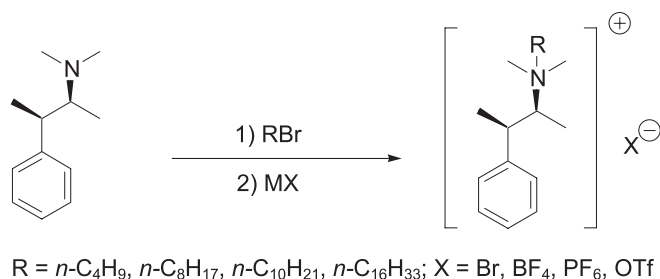
prepared *via* the efficient reaction of 1-methylimidazol with alkyl halides and terminal dihalides under solvent-free conditions. ILs were obtained in less than 2 minutes and with yields higher than 70% (Scheme 1) [28]. The same researchers published an efficient synthesis of ILs using ultrasounds as non-conventional energy source [29].



Scheme 1.

Khadilkar and Rebeiro reported, also in 2001, another microwave-assisted synthesis of ILs including imidazolium, pyridinium and lutidinium at relative large scale. In this paper, two reactions were carried out employing a modified domestic microwave oven, at 30% of the high power. In the rest of the cases, a digester microwave oven (MARS-5) with closed vessels was used for obtaining moderated to excellent yields [30].

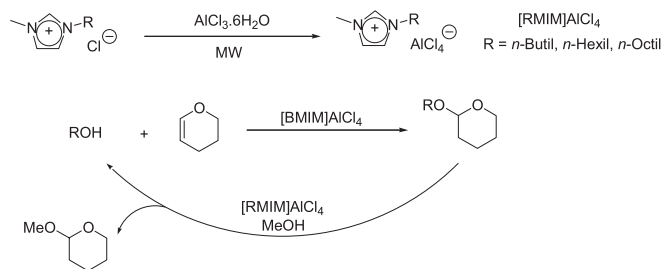
Recently, other authors have generalized the microwave-assisted synthesis of ILs to another nitrogen-containing Heterocycles [31]. Vo-Thanh et al. expanded the methodology for synthesizing chirals ILs from (1*R*, 2*S*)-*N*-methylefedrine (Scheme 2) [31e]. In this work, the two steps of synthesis (ILs containing halogen as anion and the anion interchange) were studied under microwave conditions and in both closed and open vessels. The authors present mechanistic and experimental evidences of no purely thermal microwave effect (specific MW effect) [32] for explain the observed acceleration in reaction completion respect to the conventional method.



Scheme 2.

Another procedure for the synthesis of chirals ILs was described by Bica, et al. starting from cheap chiral pool precursors camphorsulfonic acid and camphene. Several imidazolium ILs were synthesized in high overall yield. Both thermal and microwave-assisted synthesis were used in the quaternization step to obtain new chiral ionic liquids (CILs) bearing a bornyl structural motif as cation. Furthermore, these CILs were used as solvent in the Diels-Alder reaction of acrylic acid and cyclopentadiene and showed good yields and diastereoselectivities [33].

The methatesis step for introducing a new anion in halogen-based ILs under microwave conditions was firstly described by Varma and Nambooridi. Reaction time and yields were improved dramatically respect to the conventional methods [34]. In this 2002 paper, the synthesis of dialkylimidazolium tetrachloroaluminates ([RMIM]⁺AlCl₄⁻) and their application as recyclable catalyst for the efficient and eco-friendly protection of alcohols, phenols and diols as tetrahydropyranyl (THP) ethers are described. The ILs were also used for the deprotection of THP ethers without required anhydrous condition (Scheme 3) [35].



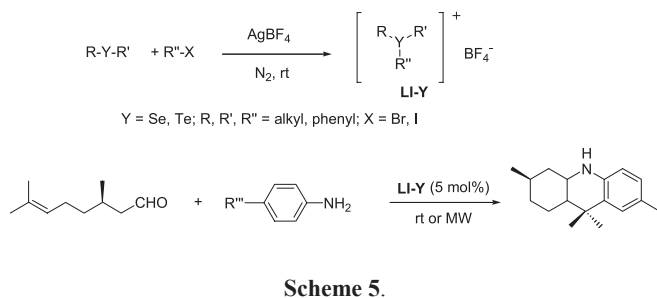
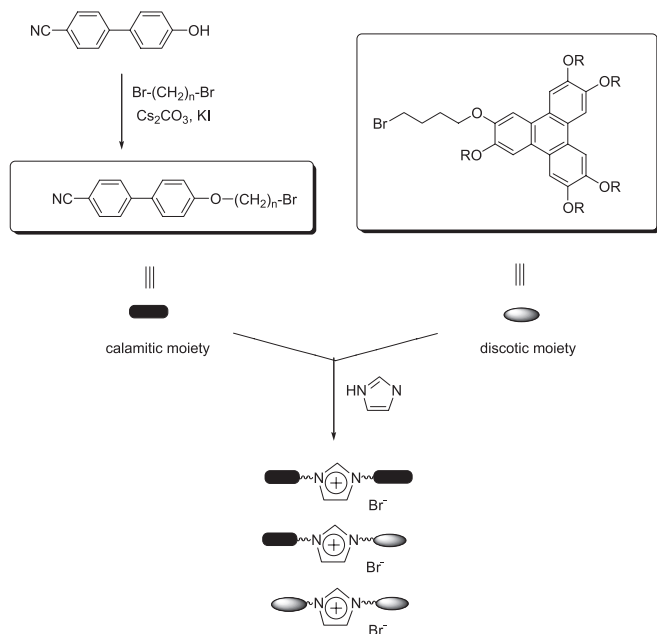
Scheme 3.

A similar work, related to the synthesis of tetrachloroindates (III) anion-based ILs and with the same application (alcohols protection as THP ethers) and also, as catalyst for cyclic carbonates synthesis, were published by Kim and Varma [36, 37], and more recently the synthesis of tetrachlorogalates as catalyst of acetalization reaction has been carried on [38].

Another simple procedure for the monotetrahydropyranylation of diols and alcohols, in excellent to moderate yields, was reported in 2006 using a catalytic amount of the acidic ILs, 1-Butyl-3-methylimidazolium hydrogensulphate ([BMIM]HSO₄) under microwave and ultrasonic irradiation. The IL was synthesized under microwave conditions and its has also been employed as catalyst on coumarins synthesis [39].

Pal and Kumar described in 2006 a microwave-assisted synthesis of novel imidazolium-based ILs crystalline dimers containing calamitic-calamitic, calamitic-discotic and discotic-discotic moieties. The most widely studied alkoxyphenyl and triphenylene units were chosen as calamitic as discotic parts, respectively (Scheme 4). Classical reactions failed to produce these dimers. The thermotropic liquid crystalline properties of these salts were investigated by polarizing optical microscopy, differential scanning calorimetry and X-ray diffractometry. Some of these salts with bromide as counter ion were found to be mesomorphic over a wide temperature range [40].

Recently, a general and easy method for the synthesis of several selenonium and telluronium salts was described. These compounds are acidic liquids at room temperature and were obtained in excellent yields. Phenyl butyl ethyl selenonium tetrafluoroborate was employed in the hetero-Diels-Alder cyclization of aryl imines derived from citronellal, affording octahydroacridines in good yields (Scheme 5) [41].

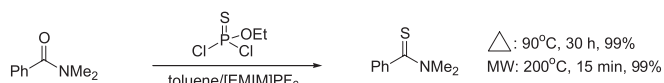


Applications of ILs on MAOS

The uses of ILs as solvent, cosolvent, additive and/or catalyst in MAOS have been gained popularity. In this century, the researchers have begun to publishing many articles and patents employing ILs in MAOS [42]. Additionally to the known catalytic properties of ILs to accelerate many organic reactions using conventional organic synthesis methodologies, since the ionic nature of ILs, these compounds absorb very efficiently microwave irradiation and can increase the rate of the organic reactions even for low polarity reaction media. To this respect, a systematic study about the heating behavior of ILs during microwave irradiation was published by Hoffmann [43].

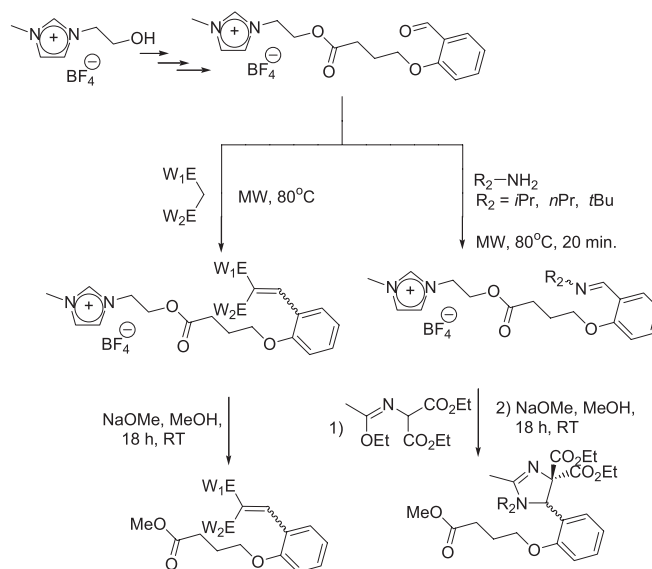
In this section, the more relevant results describing innovative applications of ILs for MAOS will be reviewed.

In 2001, Ley and coworkers published the microwave-assisted synthesis of tioamides from amides with quantitative conversion in only 15 minutes of irradiation, employing toluene as solvent containing a catalytic quantity of 1-Ethyl-3-methylimidazolium hexafluorophosphate ([EMIM]PF₆). The same reaction employing conventional heating source required 30 hours to obtain the same conversion (Scheme 6) [44].



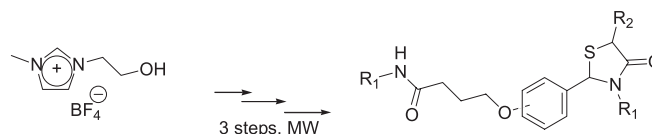
Scheme 6.

In an interesting work, Fraga-Dubreuil and Bazureau described the grafted ILs-phase supported synthesis of small organic molecules. Four formyl functionalized task-specific ILs were prepared by esterification of 1-(2-Hydroxyethyl)-3-methylimidazolium tetrafluoroborate, employing two conventional synthetic alternatives. One of the new grafted soluble ILs was used as substrate for combinatorial synthesis in liquid phase. Knoevenagel and Schiff bases formation were developed under microwave irradiation. Schiff bases were used as dipolarophiles for 1,3-dipolar cycloaddition reactions with high yield and regioselectivity. The IL was finally removed by hydrolysis and recuperated for being employed in a new reaction cycle (Scheme 7) [45].



Scheme 7.

The same authors utilized an analogue strategy for the one-step tricomponent synthesis of several 4-thiazolidinones. The final cleavage under microwave/catalysis procedure provides the expected heterocycles in high purity after flash-chromatography purification (Scheme 8) [46].



Scheme 8.

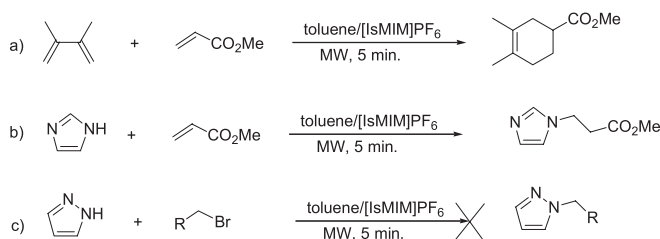
An efficient esterification using task-specific ILs were also described by Arfan and Bazureau for the reaction of carboxylic

acids with neo-pentanol under microwave irradiation. The catalyst $[\text{BMIM}][\text{HSO}_4]$ modified with 5% of concentrated sulfuric acid was reused three times without considerable loss of activity in esterification using classical heating in oil bath [47].

Another example of application of task-specific ILs is the microwave-assisted liquid-phase Gewald synthesis of 2-aminothiophenes using $[\text{2-HydeMIM}][\text{BF}_4]$ as soluble support. This new synthetic method is simple and efficient, and the products are obtained in good to excellent yields with high purities, without to need chromatographic purification [48].

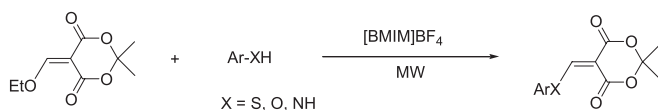
Leadbeater and Torenus [49] were the first in develop a systematic study for the application of ILs as additives for reactions carried out under microwave irradiation conditions. In this 2002 paper, the authors showed that hexane and toluene together with solvents such as THF and dioxane can be heated way above their boiling point in sealed vessels using small quantity of an ionic liquid.

Three classical reactions were studied employing toluene as solvent with a catalytic quantity of 1-Isopropyl-3-methylimidazolium hexafluorophosphate (0.2 mmol/2 mL of solvent): the Diels-Alder reaction between 2,3-dimethylbutadiene and methyl acrylate, in which the adduct was obtained in 80% after 5 minutes of microwave irradiation (Scheme 9a), Michael addition of methyl acrylate to imidazole employing triethylamine as catalyst, in which the 1,4 adduct was obtained in 75% after 5 min of microwave irradiation (Scheme 9b) and the alkylation reaction of pyrazole with an alkyl bromide (Scheme 9c). This last reaction failed under these conditions, the aryl halide reacting with the IL at the elevated temperatures used in this reaction, thus the authors suggest that the application of ILs for MAOS is not appropriated for reactions which use or generate nucleophiles such as halide ions.



Scheme 9.

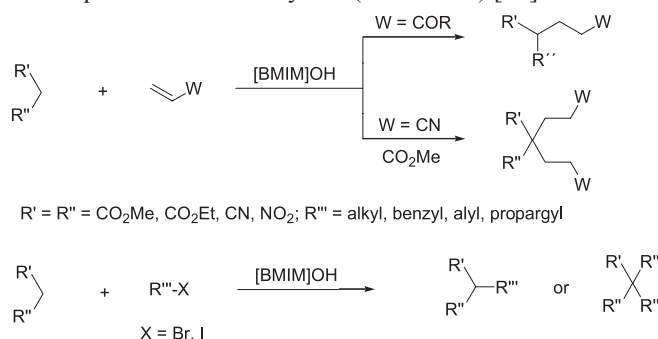
On the other hand, Guo and Yuan found that the reaction rate of nucleophilic substitution can be dramatically enhanced by microwave irradiation using $[\text{BMIM}]\text{BF}_4$ as solvent. Nucleophilic reagents (anilines, thiophenol) react with ethoxymethylene isopropylidene malonate (**1**) to give corresponding products in 5-10 min in good yields. The nucleophilic substitutions show that the order of nucleophilicity is $\text{ArNH}_2 > \text{ArS}^- > \text{ArO}^-$ when the react with **1** (Scheme 10) [50].



Scheme 10.

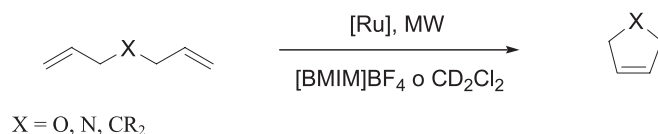
Michael addition under IL/MW technology has been reinvestigated this year, by two research groups. Zare et al. described a simple, clean and efficient procedure for microwave-assisted Michael addition of sulfonamides to α,β -unsaturated esters using zinc oxide in $[\text{BMIM}]\text{Br}$ as a new, highly efficient, green and reusable catalyst [51]. While Ranu, Banerjee and Jana studied a basic catalyst, $[\text{BMIM}]\text{OH}$ on Michael addition of active methylene compounds to conjugated ketones, carboxylic esters and nitriles. The alkylation active methylene compounds and the addition of thiols to α,β -acetylenic ketones were also studied employing the basic IL in solvent-free conditions

The Michael addition to α,β -unsaturated ketones proceeds in the usual way, giving the monoaddition products, whereas addition to α,β -unsaturated esters and nitriles leads exclusively to the bis-addition products. The α,β -acetylenic ketones undergo double conjugate addition with thiols producing β -keto 1,3-dithio-derivatives. In the alkylation reaction the acyclic 1,3-diketones are monoalkylated, whereas cyclic ketones undergo dialkylation under identical conditions. The ionic liquid can also be recycled (Scheme 11) [52].



Scheme 11.

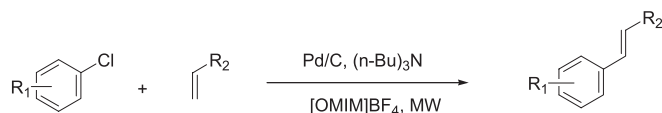
Mayo and coworkers showed that microwave heating is an efficient method for the acceleration of the ring-closing metathesis reactions of 1,6-dienes using ruthenium-based catalyst. The reaction was rapidly conducted in either IL (1-Butyl-3-methylimidazolium tetrafluoroborate) or in a microwave transparent solvent such as dichloromethane. In this last solvent the reaction temperature never exceeded 33 °C and by this fact, the author suggest that microwave energy is producing non-thermal effect, involving direct coupling to one of the two or both reactants in these transformations (Scheme 12) [53].



Scheme 12.

Kappe and coworkers studied newly the ring-closing metathesis reactions of dienes using ruthenium-based catalyst (Grubbs type II catalyst) with and without IL ([BMIM]PF₆)-doped methylene chloride, with the object to generalize the protocol for the formation of 5, 6 and 7 members heterocycles. A careful study using a monomode microwave equipment respect to the conventional reaction (cuarze recipes and oil bath) indicate that the observed rate enhancements are not the result of non-thermal microwave effect suggested by Mayo et. al. Very rapid conversions (15 seconds) were achieved utilizing 0.5 mol % of catalyst under sealed vessel microwave conditions [54].

Coupling reactions employing transition metal catalyst have also been studied using ILs under microwave conditions. For example, Larhed's [55] and She's [56] research groups have been studied the phosphine-free ligand, Palladium-catalyzed Heck arylations of olefins in presence of 1-Butyl-3-methylimidazolium hexafluorofosfate ([OMIM]PF₆) and 1-Octyl-3-methylimidazolium tetrafluoroborate ([OMIM]BF₄), respectively. Larhed and coworkers carried out the couplings efficiently in sealed tubes. Both research groups founds that the ILs phase could be recycled in five successive reactions with a little lost of activity. The product was easily removed from the reaction medium by distillation (Scheme 13)[55].



Scheme 13.

Heck reaction has also been employed for the synthesis of 3-naphthylcyclohexene by the coupling of bromonaphthalene and naphthyl triflates with cyclohexene catalyzed by palladium and nickel complex (promoted by ultrasonic and microwave in ILs). The reactions were performed with high yield and good regioselectivity. This method has advantages of environmentally benign, generality, simplicity and potential for recycling of IL and catalyst [57].

While Leadbeater et al. reported the scale-up of Heck reaction from mmol to mol scale for microwave-promoted Heck coupling of aryl iodides in open reaction vessels. Reactions are performed using 0.1 mol% palladium acetate as the catalyst, sodium carbonate and tributylamine as bases and tetrabutylammonium bromide as an additive [58].

Berthold, Schotten and Honig studied the catalytic transfer hydrogenation of different homo- and heteronuclear organic compounds in 1-Butyl-3-methylimidazolium tetrafluoroborate ([BMIM]PF₆) as solvent under microwave irradiation. Ammonium formate and triethylammonium formate were used as hydrogen source. Products were obtained with good purity in moderate to excellent yields by simple liquid-liquid extraction with methyl *tert*-butyl ether. The procedure can be applied to different functional groups and ILs/catalyst can be recycled (Table 1) [59].

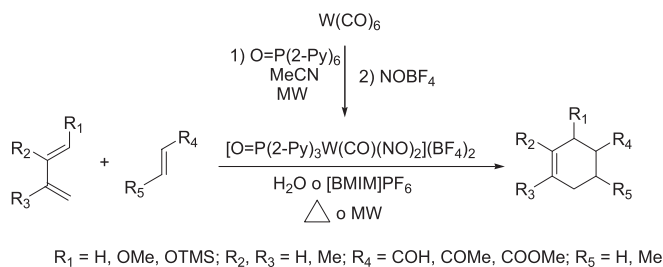
Table 1. Catalytic Transfer Hydrogenation in [BMIM]PF₆.

entry	substrate	product	yield (%) ^a
1			92 (83) ^b
2			99 (83)
3			84 (98)
4			-- (97)
5			50% of conversion (6:1:1) (97, only c)
6			0:30 (0)
7			67

^a Yield obtained using ammonium formate as a hydrogen source. ^b In bracket the yield obtained using triethylammonium formate as a hydrogen source. ^c E = CO₂Et

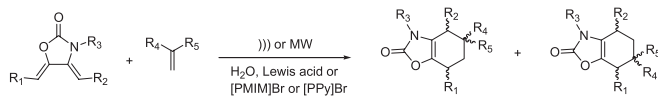
Cycloaddition reactions are one of the most studied processes employing ILs and microwave-assisted synthesis. A review about environmentally benign solvent systems toward a greener [4+2] cycloaddition process, including ILs was recently published [60].

Additionally to the examples described before, the Diels-Alder cycloaddition, under conventional heating and under microwave conditions employing organotungsten catalyst (synthesized in microwave), was published. The reactions were efficiently conducting in water and in [BMIM]PF₆. The use of the IL accelerated the reactions and the catalyst can be recycled easier (Scheme 14)[61].



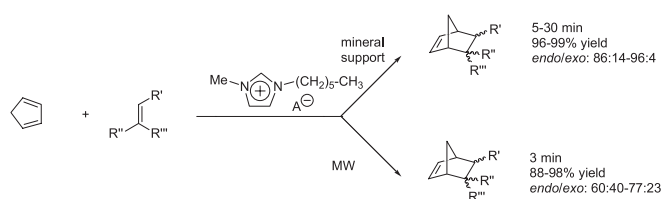
Scheme 14.

The effect of ILs in Diels-Alder cycloaddition of 2-oxazolidinones *exo*-heterocyclic dienes with several dienophiles in different reaction conditions (catalytic, thermal, employing ultrasound power and microwave conditions) was investigated. The ILs employed in this work (1-Methyl-3-pentylimidazolium bromide ([PMIM]Br) and *N*-Pentylpyridinium bromide ([PPy]Br)) were synthesized under microwave (Scheme 15) [62], but these ILs employed do not significantly enhanced the selectivity of the reactions conducted under thermal or microwave conditions, however other works have shown a remarked enhanced in *endo*-selectivity for these reactions, employing ILs as Lewis acids [63].



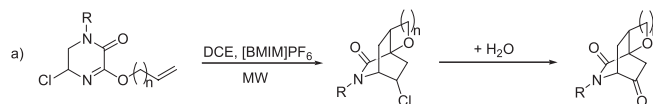
Scheme 15.

Recently, the role of mineral catalysts and microwave irradiation in ILs as recyclable media for enhancing Diels-Alder reactions, involving 1,3-cyclopentadiene and numerous dienophiles was published. The use of mineral support increase the *endo*-selectivity, while microwave-assisted synthesis reduce the reaction time. A carefully inspection to the results evidence that microwave irradiation is the driving force for the transformations and *endo:exo* selectivities are attained. Reactions were controlled over 3 minutes. It appears that none of the catalysts added exerted any noticeable influence on the stereoselection of the cycloaddition run under microwave irradiation. The coupling of ILs with microwave irradiation affords good rate enhancements, though poor stereoselection, for Diels-Alder reaction, whose completion occurs typically in a matter of a few minutes (Scheme 16) [64].

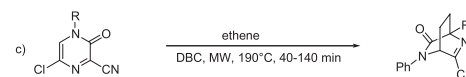
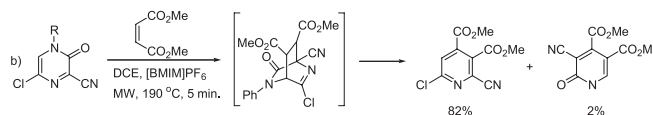


Scheme 16.

Hetero Diels-Alder (inter- and intramolecular) type reactions are another examples of reactions efficiently carried out by combination of ILs/MW. In this sense, Van der Eycken, Kappe and coworkers studied these reactions employing functionalized 2(1*H*)-pyrazinones. In this 2002 paper, the cycloaddition reactions were efficiently performed in sealed tubes, utilizing either a combination of 1,2-dichloroethane (DCE)/[BMIM]PF₆ or 1,2-dichlorobenzene. In all cases, a significant rate-enhancement using microwave conditions were observed. The starting point of these investigations involved intramolecular hetero-Diels-Alder reactions in a series of alkenyl-tethered 2(1*H*)-pyrazinones (Scheme 17a). These reactions take 2-3 days for completion by thermal heating. When intramolecular cycloaddition was carried out using methyl maleate as dienophile, tetrasubstituted pyridines were obtained by retro-cycloadditions of the intermediary adduct (Scheme 17b). In addition, the authors showed that the use of a gaseous reagent (ethane) in a sealed vessel microwave experiment may provide an alternative, more efficient method to carry out synthetic transformations in comparison to standard autoclave protocols (Scheme 17c) [65].

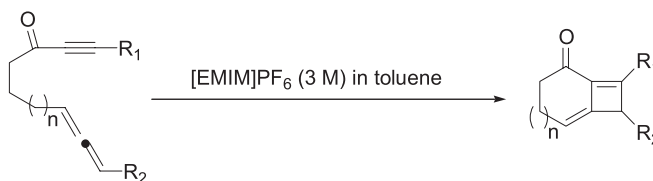


R = Ph, Bn; n = 2, 3.



Scheme 17.

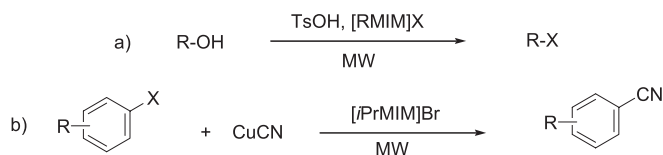
Brummond and Chen studied the [2 + 2] intramolecular cycloaddition reaction of alquynyl allenes for generating bicyclic systems containing cyclobutene. The optimal conditions were obtained when toluene doped with 1-Ethyl-3-methyl-imidazolium hexafluorophosphate (3 M) was used as solvent and the mixture was irradiated under microwave at 250-280°C (Scheme 18) [66].



Scheme 18.

ILs have also been employed as reagent and solvent in combination with microwave energy to carry out the synthesis of alkyl halides from the corresponding alcohols and in the preparation of nitriles from the corresponding aryl bromides or iodides [67]. The first reaction type was studied in three ILs ([*n*PrMIM]I, [*i*PrMIM]Br, [BMIM]Cl) that act as nucleophiles and solvent. The use of toluene as cosolvent avoids the decomposition of the ILs at high temperature (> 200°C), but the yield decreased. The reaction time can be reduced from 24-48 hours (at room temperature) [68] down to 3 minutes under microwave irradiation. The reaction works well for primary alcohols but fails when secondary or tertiary alcohols are employed as substrates. Reactions were completed in 3 minutes under microwave irradiation (Scheme 19a) [67].

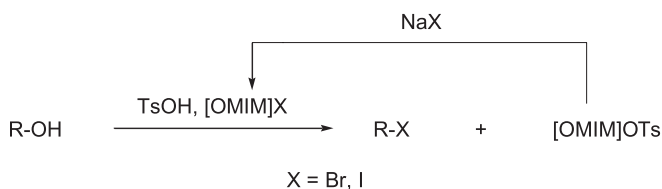
While in the synthesis of aryl nitriles from the corresponding halides (Rosenmund-von Braun reaction), the reaction time can be reduced from 24 hours (conventional heating) [69] to 3 minutes under microwave irradiation. The reaction was study in [*i*-PrMIM]Br and [BMIM]PF₆, but only the first IL generated the desirable product employing bromide and iodide substrates (Scheme 19b) [67].



Scheme 19.

We have developed a simple and efficient method for the esterification of various organic acids with C4-C18 alcohols using the 1-octyl-3-methyl-imidazolium tetrafluoroborate-*para*-toluenesulphonic acid (OMIM/BF₄-PTSA) couple, without organic solvent, either by classic heating or by microwave irradiation. The use of the OMIM/BF₄-PTSA couple presents considerable advantages: high yield, low temperature, short reaction time, isolation of the ester by simple decantation, easy reuse of the catalyst couple.

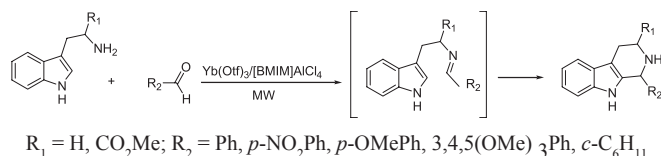
Almost simultaneously to the paper of Leadbeater [67]; Nguyen, Matondo and Baboulène, reported a similar methodology for the conversion of fatty alcohols in the corresponding alkyl halides, employing 1-Octyl-3-methylimidazolium bromide ([OMIM]Br) and iodide ([OMIM]I) in the presence of *p*-TsOH. Excellent yield were reported for both thermal heating and microwave-promoted synthesis. The ILs were recuperated and reused (Scheme 20) [70].



Scheme 20.

Aryl and arylvinyl nitriles have also been prepared in good yields from the corresponding bromides with potassium hexacyanoferrate (II) using palladium-catalyzed reactions in ILs under microwave irradiation [71].

Pictet-Spengler's reaction has been explored for the preparation of tetrahydro- β -carboline under LI/MW conditions. In this work a parallel evaluation of several catalyst was carried out. The authors found that the IL [BMIM]BF₄ had moderated activity, while [BMIM]AlCl₄ resulted a very active catalyst, obtaining the higher stereoselectivity (*trans/cis*, 1:1.6). The microwave reaction was completed in 30 min, employing both, aliphatic and aromatic amines and 10 mol% of Yb(OTf)₂ and 50 mol% de [BMIM]Cl-AlCl₃, (*N* = 0.5), obtaining the tetrahydro- β -carboline in one-step in yields higher than 85%, even when amines with low nucleophilic character were utilized (Scheme 21).



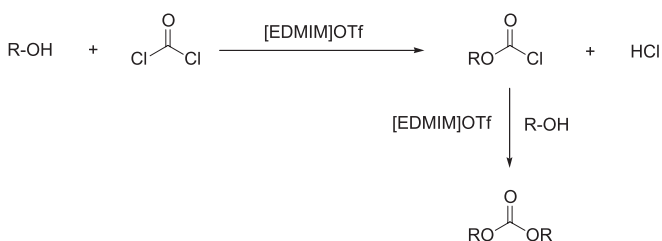
Scheme 21.

Some other name reactions studied under IL/MW technology are described in Table 2.

Table 2. Some name reactions studied employing IL/MW technology.

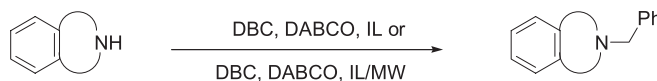
Name reaction	Catalyst /IL	Reference
Beckman rearrangement	5 mol% H ₂ SO ₄ /[BMIM]X X = SbF ₆ , BF ₄ , PF ₆ , OTf	[73]
Pechmann	[BMIM]HSO ₄	[74]
Stetter	imidazolium-type ILs/ thiazolium salts, Et ₃ N	[75]
Mannich condensation	CuCl (I)/[<i>i</i> -ProMIM]PF ₆	[76]
Knoevenagel	Ethylammonium nitrate, [BMIM]BF ₄ or [BMIM]PF ₆ rt/[BMIM]BF ₄	[77] [78]
Biginelli	task-specific ILs	[79, 80]
Tsuji-Trost	Pd(OAc) ₂ /[EMIM]BF ₄ / H ₂ O	[81]
Baylis-Hillman (assymetric)	<i>N</i> -alkyl- <i>N</i> - methylephedrinium	[82]
Hantzsch	task-specific ILs	[80]

Phosgenation of alcohols is another reaction carried out successfully under IL/MW conditions. The phosgenation of *n*-butanol was achieved in one-pot reaction and in a two-chamber reactor in which freshly produced phosgene gas was bubbled through the educt solution. New catalyst such as phenantroline, benzyltriethylammonium chloride and 1,3-dimethyl-imidazolium bistrifluoromethanesulfoneimide ([EDMIM]OTf) were employed for the decomposition of triphosgene, alone or in combination with activated charcoal, which acted as microwave absorber (Scheme 22) [83].



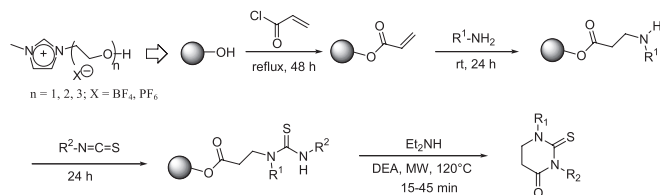
Scheme 22.

IL/MW can accelerated other reactions like *N*-alkylation of cyclic imines with aryl chlorides [84], aromatic nucleophilic substitution of chloronitrobenzenes with amines [85], and *N*-benzylation of benzoazoles employing dibenzyl carbonate (DBC). In the last case, ILs dramatically increased the reaction yield and time from 24-96 hours (without ILs) to 0.5-3 hours (with ILs) and 6-12 minutes with IL/MW (Scheme 23) [86].



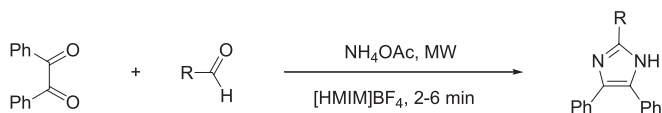
Scheme 23.

Multicomponent reactions have been widely explored under IL/MW conditions, for example Hakkou and coworkers prepared 2-tioxo-tetrahydropyrimidin-4-(1*H*)-ones employing a ionic liquid phase organic synthesis strategy. Starting from *N*-poly(ethyleneglycol)imidazolium type ILs, which were functionalized with acryloyl chloride (96-98% yield) an the PEG-IL acrylate products were employed as substrates for the three-steps synthesis of heterocyclic compounds. In the last step, final products were obtained by microwave-promoted cyclization of thioureido esters under solvent-free conditions (Scheme 24) [87].



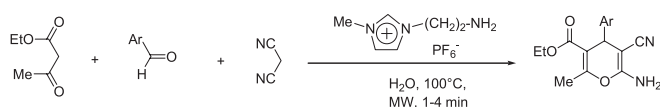
Scheme 24.

The three-component synthesis of 2,4,5-trisubstituted imidazoles, a typical acid-catalyzed reaction, could be conducted successfully with good to excellent yields in a neutral ILs, 1-Methyl-3-heptyl-imidazolium tetrafluoroborate ([HMIM]BF₄), under solvent-free and microwave-assisted conditions. The reaction can also be applied to the synthesis of bisimidazoles from benzyl and dialdehydes in only 4 minutes, while the same reaction by conventional heating employing acetic acid as catalyst required 5 h. The combined merits of microwave irradiation and ionic liquid make the three-component condensation with safe operation, low pollution, and rapid access to products with a simple workup. (Scheme 25) [88].



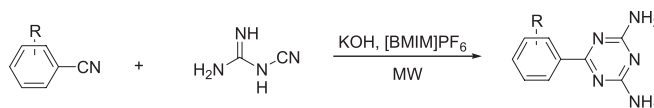
Scheme 25.

Employing a tricomponent strategy, Peng and Song have been found that the mixture of catalytically active 1-Methyl-3-(2-aminoethyl)imidazolium hexafluorophosphate and water is an environmentally friendly and recyclable reaction medium in the synthesis of 4*H*-pyrans derivatives under computer-controlled microwave irradiation (Scheme 26) [89].



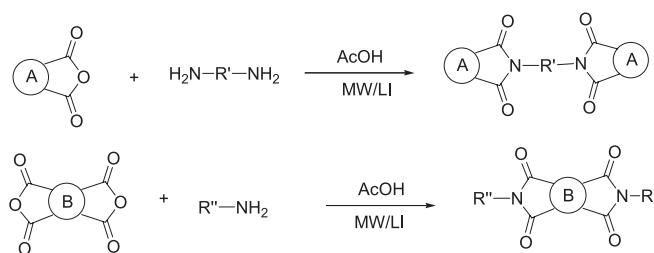
Scheme 26.

The same authors published a “green” and efficient methodology for microwave-promoted synthesis of 6-aryl-2,4-diamino-1,3,5-triazines from the corresponding aryl nitriles and cyanoguanidines in [BMIM]PF₆ (Scheme 27) [90].



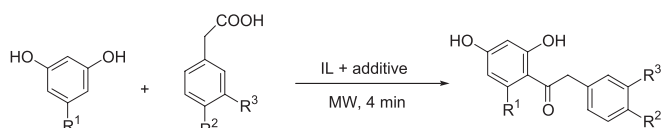
Scheme 27.

A versatile, fast and efficient microwave-assisted synthetic procedure for the preparation of bisimides is described. This procedure can be applied employing either diamines (aliphatic or aromatic) or dianhydrides as reagents. The use of ILs as cocatalyst increased the rate and yields of these reactions significantly. The products were obtained in good to excellent yields within 10 minutes of irradiation, and with high purity after a simple work-up (Scheme 28) [91].



Scheme 28.

A microwave-promoted synthesis of polyhydroxydeoxybenzoins and arylpropanones was developed, using bis{(trifluoromethyl)sulfonyl}amine (HNTf₂) or BF₃-Et₂O in an IL solvent, through a Friedel-Craft acylation reaction in only 4 min at moderate temperature in moderated to good yields (55-88%) (Scheme 29) [92].



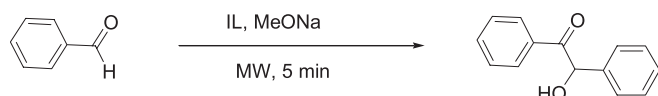
Scheme 29.

Metal-free phthalocyanine derivatives have also been synthesized in very short times with high yields in the presence of 1,1,3,3-tetramethylguanidinium trifluoroacetate (TMGT) as an ionic liquid or tetrabutylammonium bromide (TBAB) as a phase transfer reagent under both classical heating conditions and using microwave irradiation. The best results were obtained with ionic liquid. Both the ionic liquid and phase transfer reagent can be recycled for subsequent reactions and reused without appreciable loss of efficiency [93].

The IL/MW technology has also been applied for oxidation of benzylic alcohols to their corresponding carbonyl compounds using KIO₄ as oxidant agent. The method is chemoselective, straightforward, and rapid. The reaction has been carried out with excellent yields and short reaction times [94].

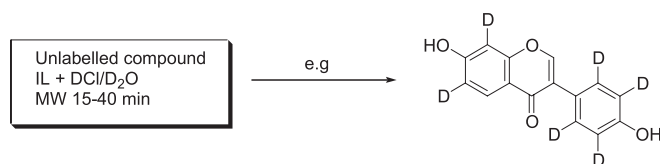
A free-solvent benzoin condensation was performed with several imidazolium-based ILs as catalysts under microwave irradiation. The product was obtained with good yield (up to 97%) and purity, in a very short time. Microwave-assisted

synthesis increased notably the yield of the reaction respect to conventional heating. This method gives very good results for chloride and bromide based ILs catalyst but is also possible with non-halide ILs (Table 3). Moreover, the work-up only requires the use of water, giving a green touch to the overall process. (Scheme 30) [95].



Scheme 30.

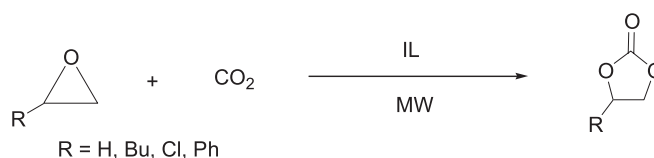
IL/MW can be employed for deuterolabeling of polyphenols. Postsynthetic regioselective aromatic ring H/D exchanges in polyphenolic compounds are rapidly performed in high yields and isotopic purities in IL and DCl/D₂O under microwave irradiation. Other C-H bonds, including benzylic and lactone alpha-carbonyl sites, are not affected (Scheme 31) [96].



Scheme 31.

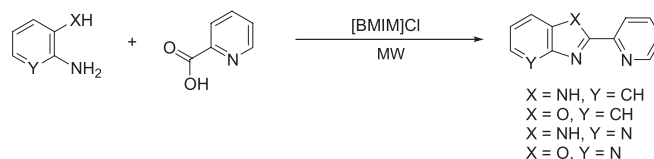
The solvent-free synthesis of cyclic carbonates from CO₂ and epoxides in the presence of a novel catalyst consisted of zinc phenosulfonate octahydrate and Bu₄NBr were carried out under microwave irradiation with controlled temperature and pressure. In comparison with classical heating in oil bath, microwave was demonstrated to be a more effective energy source. Pseudo-first order kinetic treatment revealed that the observed reaction acceleration under microwave irra-

diation mainly derived from the non-thermal effects of microwave, which leads to an obvious decrease in activation energy (Scheme 32) [97].



Scheme 32.

An efficient and fast procedure for the synthesis of 2-(2-Pyridyl)azoles, from *o*-substituted aromatic amines and picolinic acid, was described using ILs as catalysts under microwave irradiation (Scheme 33) [98]. These compounds were evaluated as corrosion inhibitors for oil refinery environments. The results were rationalized by quantum chemical study [99].



Scheme 33.

The debromination of α -bromoketones with 1-Methyl-3-pentylimidazolium tetrafluoroborate, ([PMIM]BF₄) under microwave irradiation was investigated. By controlling the reaction time gem- α -dibromoketones are selectively debrominated to either monobromo or debromoketones. The α -monobromo- and α -moniodoketones are dehalogenated while the corresponding chloroketones remain inert. This procedure can lead to the selective removal of a bromide in the presence of a chloride functionality (Scheme 34a). This reaction

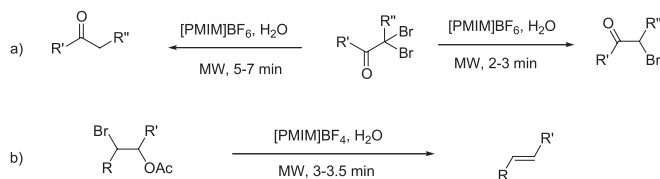
Table 3. Solvent-free benzoin condensation using non-halide ILs as catalyst.

Entry ^a	Catalyst (2 mol.%)	Activation method	Yield (%) ^b	Benzoic acid (%) ^c
1	OMIOTf	Thermal 150 °C	18	26
2	OMIOTf	MW (20 W) up to 150 °C	70	0
3	OMIPF ₆	Thermal 150 °C	13	61
4	OMIPF ₆	MW (20 W) up to 150 °C	65	0
5	OMINTf ₂	Thermal 150 °C	6	0
6	OMINTf ₂	MW (20 W) up to 150 °C	55	0
7	OMIBF ₄	Thermal 150 °C	0	0
8	OMIBF ₄	MW (20 W) up to 150 °C	29	0
9	BMICF ₃ CO ₂	Thermal 150 °C	5	0
10	BMICF ₃ CO ₂	MW (20 W) up to 150 °C	76	0

^a General procedure: 22 mmol of benzaldehyde; 10 mol.% MeONa, 2 mol.% IL, 150 °C (oil bath) or temperature up to 150 °C, 20 W of microwave power, 5 min.

^b Isolated yield.

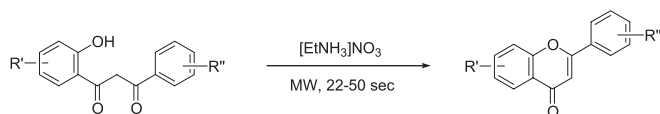
was also successfully used for the stereoselective formation of (*E*)-alkenes by debromination-elimination of activated *vic*-bromoacetates (Scheme 34b). These reactions do not require any organic solvent, metal or conventional reducing agent. In general, reactions by this methods are very clean, high yielding and fast. The IL works here as catalyst, as well as reaction medium and is recycled without any appreciable loss of its catalytic efficiency [100].



Scheme 34.

In 2005, the same authors published a related work about a green protocol for the stereoselective debromination of vicinal dibromides [101].

Recently, the applications of ILs/MW technology have been expanded to a new environmental friendly technology, such as the aqueous [BMIM][BF₄] as green solvent in microwave-assisted clean synthesis of 1*H*-benzo[*f*]chromene derivatives [102], a novel method for fluorination of halopyridazine derivatives with potassium fluoride [103], and a high yielding and fast method for the smooth conversion of substituted 1-(2-Hydroxyphenyl)-3-phenyl-1,3-propanediones to the corresponding 2-phenyl-4*H*-chromen-4-ones with yield higher than 80% in very short reaction time, under microwave irradiations using the IL [EtNH₃]⁺NO₃⁻ as solvent and catalyst, which can be recycled and reused several times (Scheme 35) [104].



Scheme 35.

ILs have also been explored as template, solvent and catalyst in microwave-assisted polymer synthesis, such as the synthesis optically active poly(amide-imide)s from L-methinine derivatives [105], in the preparation of two new isostructural coordination polymers with novel anionic metal-organic frameworks [106], the living cationic ring opening polymerization of 2-ethyl-2-oxazoline [107], and in the ring-opening polymerization of ϵ -caprolactone [108].

A systematic study about the extraction of sulfur compounds from natural gasoline by liquid-liquid extraction procedure was recently realized. 90 ILs were prepared and evaluated, some of them synthesized under microwave irradiation. Some ILs were highly efficient for removing sulfur compounds from natural gasoline and can be recuperated and reused in several extraction cycles [109].

Conclusions

The examples covered in this review clearly demonstrate the potential of MAOS using ILs as solvent, cosolvent, additives and/or catalyst. Many well known and some new reactions have been rewritten using MW/LIs technology with evident advantages in most of the cases. The synergies arising from the combined use of MW and ILs will certainly go a long way to meet the increasing demand for environmentally benign chemical processes.

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