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Ionic Liquids as Doping Agents in Microwave Assisted Reactions

Marcos A. P. Martins, Jefferson Trindade Filho,
Guilherme S. Caleffi, Lilian Buriol and
Clarissa P. Frizzo

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1. Introduction

The use of microwave (MW) irradiation as a tool for organic synthesis has been a fast growth area [1-8]. Several examples have shown that the application of MW irradiation reduces the reaction time, increases the product yield and sometimes results in a different product distribution compared to conventional thermal heating method [1-6,9-20]. The rate acceleration observed in organic reactions using MW irradiation is due to material-wave interactions leading to thermal and nonthermal effects. The thermal effects result from a more efficient energy transfer to the reaction mixture, which is known as dielectric heating. This process relies on the ability of a substance (solvent or reactant) to absorb MW and convert them into heat. The reaction mixture is heated from the inside since the MW energy is transferred directly to the molecules (solvent, reactants, and catalysts). This process is known as 'volumetric core heating' and results in a temperature gradient that is reversed compared to the one resulting from conventional thermal heating [1,9-14]. Nonthermal effects result in differences in product distributions, yields, and reaction times. They may result from the orientation effects of polar species in the electromagnetic field that makes a new reaction path with lower activation energy [9-14, 21-23]. It has been suggested [24] that MW activation could originate from hot spots generated by dielectric relaxation on a molecular scale. Currently, thermal and nonthermal effects are being extensively studied mainly to verify the existence or not of nonthermal effects [21-23].

Several studies have reported the application of ionic liquids (ILs) in different areas and, in particular, their use in organic reactions [25-33]. ILs are generally defined as liquid electro-

lytes composed entirely of ions. Occasionally, a melting point criterion has been proposed to distinguish between molten salts and ILs ($\text{mp} < 100\text{ }^{\circ}\text{C}$). However, both molten salts and ILs are better described as liquid compounds that display ionic-covalent crystalline structures [34-35]. Suitably selected, many combinations of cations and anions allow the design of ILs that meets all the requirements for the chemical reaction under study; based on this, they are also known as 'designer solvents' [36]. Properties such as solubility, density, refractive index, and viscosity can be adjusted to suit requirements simply by making changes to the structure of the anion, the cation, or both [37-43].

The junction of the use of MW irradiation with the use of ILs provides a method of high interest in organic synthesis. ILs interact very efficiently with MW irradiation through the ionic conduction mechanism [7-8] and are rapidly heated at rates easily exceeding $10\text{ }^{\circ}\text{C}$ per second [44-50]. Despite few reports on the exact measurement of their dielectric properties and loss tangent values, the experimentally attained heating rates of ILs applying MW irradiation attest to their extremely high MW absorptivity [46,51]. This ability allows that small amounts of ILs can be employed as additives in order to increase the dielectric constant of nonpolar solvents characterizing them as doping agents [52-57]. In particular, ILs can be used as support in the synthesis of organic compounds which are carried out using MW irradiation and less polar solvents. Research groups have used ILs as doping agents for MW heating of otherwise nonpolar solvents such as hexane, toluene, tetrahydrofuran, and dioxane [52-57]. Thus, in view of the good relation between MW and IL, the following topics will be discussed in this chapter: (i) behavior of the solvents under MW environment with emphasis in the heating effects of adding a small quantity of ILs in solvents with different loss tangent, such as *N,N*-dimethyl formamide (DMF), acetonitrile (ACN), hexane (HEX), toluene (TOL), tetrahydrofurane (THF); (ii) ILs as doping agents in MW assisted reactions especially in *N*-alkylation reaction of pyrazole with alkyl halides (Figure 1).

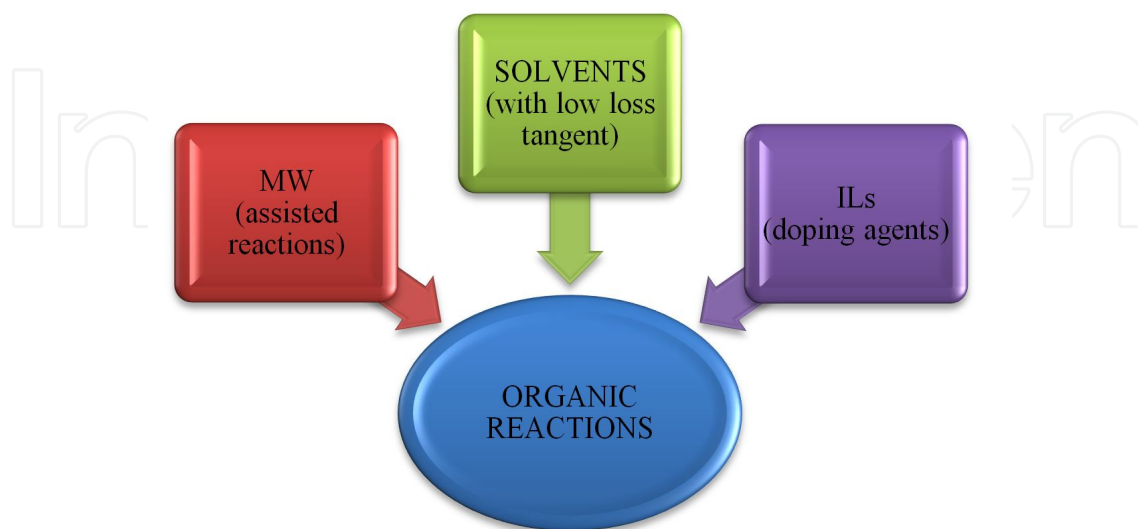


Figure 1. Ionic Liquids as doping agents in microwave assisted reactions.

2. Behavior of the Solvents Under Microwave Environment

Several organic solvents are used in various types of organic reactions under MW irradiation. The particular ability of the solvents to convert electromagnetic energy into thermal energy is directly related to their dielectric properties. The magnitude of the heating efficiency, in the specific temperature and frequency, is determined by the so-called 'loss tangent' ($\tan \delta$), whose formula is represented by Eq. 1 [52].

$$\tan \delta = \frac{\epsilon''}{\epsilon'} \quad (1)$$

In Eq. 1, ϵ'' is the dielectric loss and ϵ' is the dielectric constant. A reaction medium with a high $\tan \delta$ at the standard operating frequency of a MW synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating. Solvents used for MW synthesis can be classified as high with $\tan \delta > 0.5$, medium with $\tan \delta 0.1 - 0.5$, and low MW absorbing with $\tan \delta < 0.1$ (Table 1) [14,58]. In general, the reactions which used solvents with a high $\tan \delta$ have a good absorption of MW irradiation and, accordingly, an efficient heating [8,59,60]. Solvents such as DMSO and DMF are essential to reactions performed in MW. While these are great solvents for performing the reaction, the subsequent workup procedure is difficult to remove them due to their high boiling point and miscibility with the product [53]. Thus, in certain situations, it is convenient to use solvents which are less polar such as THF, TOL and HEX [14,58,59-60]. However, it is necessary to use a heating agent for the reactions carried out in solvents with low absorption in the MW irradiation. ILs, for instance, can be added to the reaction medium to increase the absorbance level of the MW irradiation [51,59]. Therefore, the use of ILs appears as a support to increase the temperature of the reactions carried out in a MW transparent solvents [53].

Solvent	$\tan \delta$	Solvent	$\tan \delta$
Ethylene glycol	1.350	1,2-Dichloroethane	0.127
Ethanol	0.941	Water	0.123
Dimethyl sulfoxide	0.825	Chloroform	0.091
Methanol	0.659	Acetonitrile (ACN)	0.062
1,2-Dichlorobenzene	0.280	Tetrahydrofurane (THF)	0.047
Methylpyrrolidone	0.275	Dichloromethane	0.042
Acetic acid	0.174	Toluene (TOL)	0.040
N,N-Dimethylformamide (DMF)	0.161	Hexane (HEX)	0.020

Table 1. Loss tangent of several solvents [59-60].

3. Heating Effects of Adding a Small Quantity of Ionic Liquid in Solvents

Systematic studies on temperature profiles and the thermal stability of IL under MW irradiation conditions were studied [52]. In these studies it was found that even the addition of a small amount of an IL resulted in dramatic changes in the heating profiles due to changes in the overall dielectric properties of the reaction medium.

Leadbeater and Torenus [53] studied the heating and contamination effects of several ILs in less polar solvents, such as HEX, TOL, THF and dioxane (DIO) (Figure 2) under MW irradiation. These authors have shown that all solvents used can be heated way above their boiling point in sealed vessels using a small quantity of an IL, thereby allowing them to be used as media for MW assisted chemistry. Table 2 shows the temperatures reached for pure solvents and for doped solvents with ILs using 200 W of power under MW irradiation.

The effects of varying the quantity of IL used to the solvent heating were investigated. The authors found that the best condition used was 2 mL of solvent and 0.2 mmol of IL, resulting in rapid heating. In these studies the contamination, if any, of the parent solvent with the IL or any decomposition products formed as they are heated were also studied [53].

Results showed that both [BMIM][PF₆] and [BMIM][BF₄] proved to be useful in MW heating of solvents, with [BMIM][PF₆] being more effective (Table 3). There was no contamination of the solvent when using [BMIM][PF₆] with any of the solvents screened or when [BMIM][BF₄] was used with HEX. There was contamination due to the decomposition of [BMIM][BF₄] when used with TOL or DIO; the extent was much less in the case of the latter. The [BMIM][BF₄] was slightly soluble in THF thus in this case the only source of contamination at the end of the heating experiments was a trace of the parent IL rather than any decomposition. To the experiments, 100 W of the power was used [53].

Leadbeater *et al.* [54] also investigated the decomposition of some ILs and found out that when the IL was heated above 200 °C, decomposition occurred to give an alkyl halide and alkyl imidazole as shown in Scheme 1. Halide ion (X⁻) acts as a nucleophile in attaching the cation with the subsequent elimination of alkyl-X. This decomposition was verified for elevated temperatures, which was not totally unexpected.

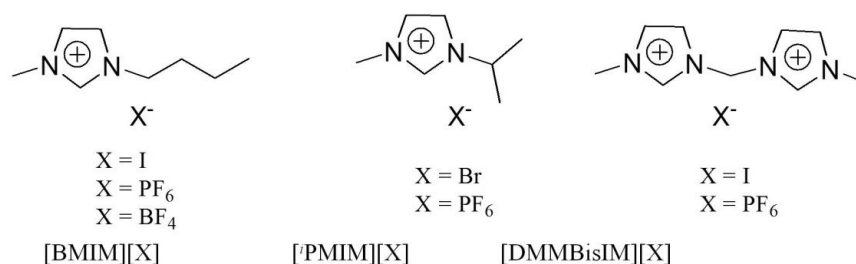


Figure 2. Ionic liquids used as doping agent.

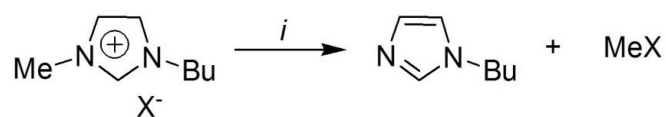
Solvent	IL Added	T(attained) (°C)	Time (taken) (s)	T (without IL) (°C)	Solvent Boiling Point (°C)
HEX	[BMIM][I]	217	10	46	69
	[<i>i</i> PMIM][Br]	228	15		
TOL	[BMIM][I]	195	150	109	111
	[<i>i</i> PMIM][Br]	234	130		
THF	[BMIM][I]	268	70	112	66
	[<i>i</i> PMIM][Br]	242	60		
DIO	[BMIM][I]	264	90	101	101
	[<i>i</i> PMIM][Br]	246	90		

Table 2. The Microwave Irradiation Effects of Adding a Small Quantity of ILs in Less Polar Solvents [53].

Solvent	IL Added	T. attained (°C)	Time Taken (s)	Level of Contamination
HEX	[BMIM][PF ₆]	279	20	None
	[<i>i</i> PMIM][PF ₆]	90	300	None
	[BMIM][BF ₄]	192	60	None
TOL	[BMIM][PF ₆]	280	60	None
	[<i>i</i> PMIM][PF ₆]	79	120	None
	[BMIM][BF ₄]	165	90	Contaminated
THF	[BMIM][PF ₆]	231	60	None
	[BMIM][BF ₄]	95	50	contaminated ^b
DIO	[BMIM][PF ₆]	149	100	None
	[BMIM][BF ₄]	184	120	Contaminated

^b[BMIM][BF₄] is slightly soluble in THF and so cannot totally be removed; thus contamination is due to [BMIM][BF₄] rather than decomposition.

Table 3. Microwave irradiation effects in the presence of a small quantity of ILs in less polar solvents [53].



X = Cl, Br, I

i: MW

Scheme 1.

Hoffmann *et al.* [61] showed that ILs of the 1,3-dialkylimidazolium-type revealed (Figure 3) great potential for the application of MW for organic synthesis. These authors verified that the increase of MW power resulted in a drastic decrease in heating time.

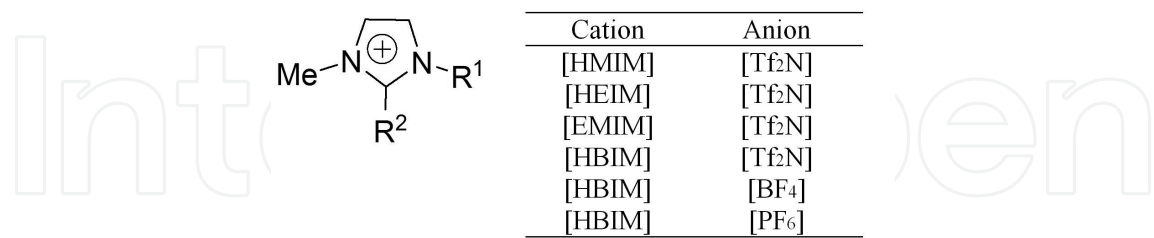


Figure 3. Ionic liquids used in the study [61].

A supplementary investigation covered the heating behavior of ILs as doping agent when mixed with solvents less polar in MW irradiation such as TOL and cyclohexane (100 mL of solvent in 1 mL, 3 mL and 5 mL of IL) (Table 4). Therefore, the authors concluded that small amounts of ILs are necessary to significantly reduce the heating time of TOL or cyclohexane under MW conditions. An increase in the MW power generates a reduction in heating time (Table 4). Also in this case, heating time approaches a limiting value even with an increase of the MW power. This was also true for the addition of ILs to both non-polar solvents (TOL and cyclohexane).

IL	Power (W)	Ht _(35-105°C/s) (TOL : IL (mL))		
		100 : 1	100 : 3	100 : 5
[HMIM][Tf ₂ N]	300	318	90	70
[HMIM][Tf ₂ N]	400	167	66	53
[HMIM][Tf ₂ N]	500	112	54	39
[HBIM][PF ₆]	300	548	168	143
[HBIM][PF ₆]	400	319	126	92
[HBIM][PF ₆]	500	229	88	86

Table 4. Heating times (Ht) of toluene/ionic liquid-mixtures.

Following the direction of these studies, we also performed some experiments using ILs as doping agents with several solvents under MW irradiation. The objective of this study was to check if the data of our MW equipment are in accordance with the data already published. Thus, we performed investigations of power profiles in different solvents with distinguished loss tangent values as DMF, ACN, THF, TOL and HEX in the presence of small quantities of [BMIM][BF₄] as doping agent. The solvents doped were submitted under MW

irradiation in an attempt to reach a temperature of 150 °C (temperature which may be used in organic reactions) [62]. For this, we used various concentrations of IL in different solvents, as shown in Table 5. After reaching the desired temperature, the doped solvents were irradiated for 5 min and we verified that lower concentrations of IL required higher power for all solvents tested (Table 5). During the 5 min of MW irradiation the power remained substantially constant. Solvents with the low loss tangent such as HEX and TOL achieved only 99 and 108 °C, respectively, even though 300 W of power was applied.

Entry	Solvent	[BMIM][BF ₄] (mmol.mL ⁻¹)	Power (W)
1	DMF	0.057	20.402
2	DMF	0.107	18.679
3	DMF	0.196	16.887
4	DMF	0.397	15.895
5	ACN	0.048	38.967
6	ACN	0.104	31.229
7	ACN	0.205	30.478
8	ACN	0.407	29.402
9	THF	0.063	240.079
10	THF	0.103	185.834
11	THF	0.218	112.582
12	THF	0.401	69.415
13	TOL	0.045	- ^b
14	TOL	0.102	119.429
15	TOL	0.197	67.805
16	TOL	0.403	47.317
17	HEX	0.049	- ^c
18	HEX	0.105	130.718
19	HEX	0.210	68.858
20	HEX	0.398	60.301

^aIn a sealed vessel, under simultaneous cooling, 150 °C for 5 min, temperature was measured with fiber-optic probe. ^bAchieved 108 °C, 300 W, 20 min. ^cAchieved 99 °C, 300 W, 20 min.

Table 5. Power dependence of IL concentration in some solvents^a.

Figure 4 illustrates the dependence between the concentrations of [BMIM][BF₄] in the solvents and the power irradiated by MW equipment. At low concentrations of [BMIM][BF₄] (~0.05 mmol.mL⁻¹) a significant increase in the power is required to maintain the temperature of 150 °C. Another point is that, to maintain the temperature of 150 °C, solvents such as

DMF and ACN did not require substantial variation of power as that found to HEX, TOL and THF when the concentration of IL ranged from $\sim 0.05 \text{ mmol.mL}^{-1}$ to $\sim 0.4 \text{ mmol.mL}^{-1}$. These data corroborate previous studies reported [53,61] and highlight the efficiency of [BMIM][BF₄] as doping agent of poorly MW absorbing solvents.

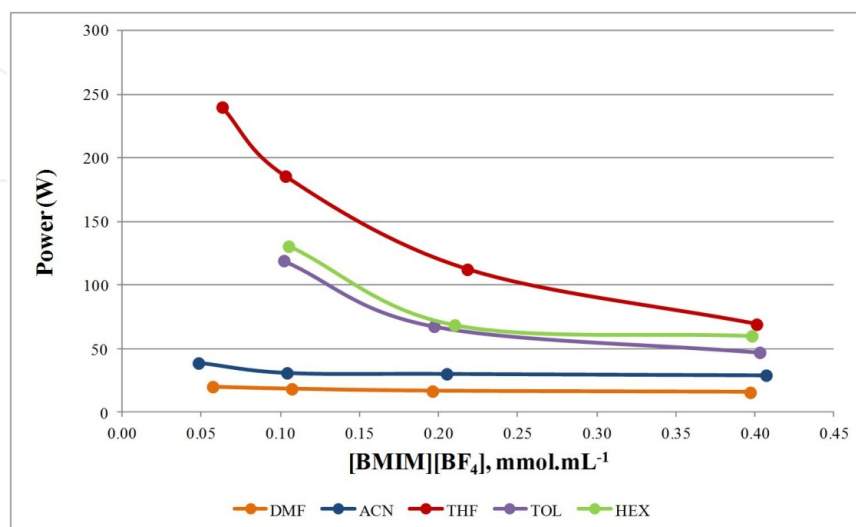
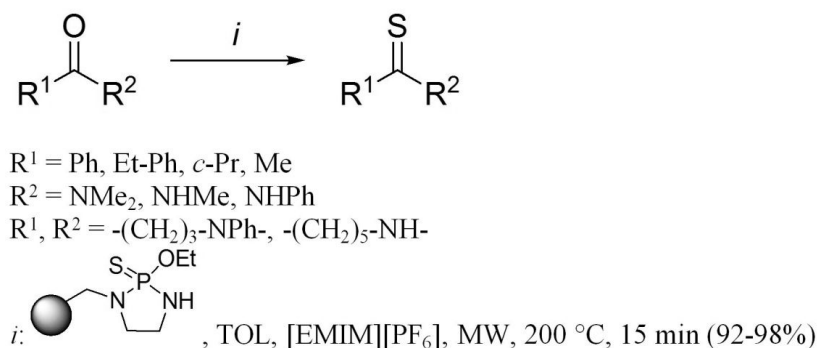


Figure 4. Power profiles of solvents with different concentrations of [BMIM][BF₄].

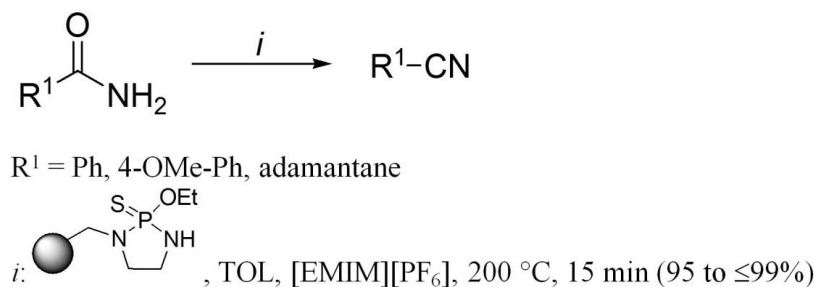
4. Ionic Liquids as Doping Agents (ILDA) in Microwave Assisted Reactions

The efficient use of ILs as a doping agent in reaction under MW irradiation was firstly introduced by Ley *et al.* [55]. The authors described the synthesis of thioamides from the secondary or tertiary amides (Scheme 2) and nitriles from primary amides (Scheme 3) in presence of thio-phosphorylated amine resin using small quantity of IL [EMIM][PF₆] (120 mg) in TOL (2.5 mL).



Scheme 2.

Protocols used the reactants thiophosphorylated amine resin and secondary or tertiary amides in a molar ratio of 1:3-20, respectively, to obtain thioamides, and used the reactants thiophosphorylated amine resin and primary amides in a molar ratio of 1:3.5, respectively to furnish nitriles. Reactions were carried out under both MW irradiation at 200 °C for 15 min to obtain the thioamides in 92-98% (Scheme 2) and nitriles in 95 - < 99% yields (Scheme 3). Acetonitrile was also investigated as an alternative MW absorbent and proved to be effective, in spite of being less efficient than the IL.

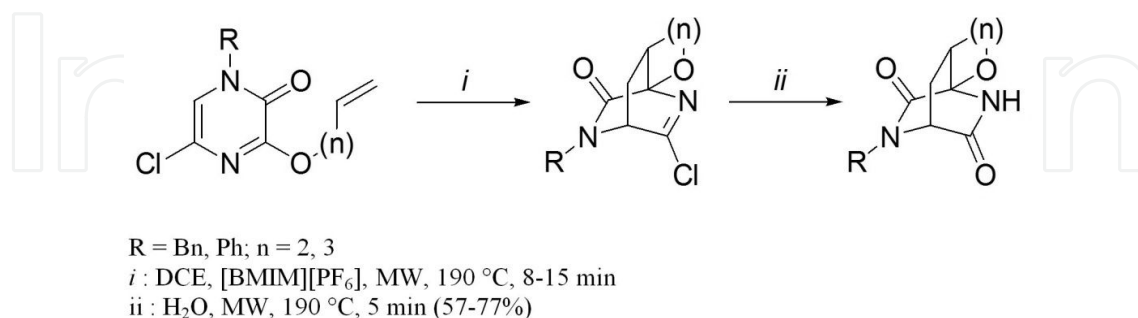


Scheme 3.

Eycken *et al.* [56] initially investigated the intramolecular hetero-Diels-Alder reaction in a series of 2(1*H*)-pyrazinones to obtain the chloro-bicycles and dione-bicycles, as showed in Scheme 4. In their initial experiments they used pyrazinone ($\text{R} = \text{Bu}$, $n = 2$) as a model substrate involving DCE as solvent to obtain the chloro-bicycles ($\text{R} = \text{Bu}$, $n = 2$). Using a preselected maximum temperature of 190 °C (300 W maximum power), neat DCE could be heated to ca. 170 °C within 10 min under sealed vessel conditions. Prolonged time heating is needed to reach higher temperatures. In an effort to promote the enhance of the maximum attainable reaction temperature, the solvent (DCE) was doped with different amounts of [BMIM][PF₆]. Adding 0.035 mmol of IL to the neat solvent (2 mL of DCE), the preselected temperature of 190 °C could be reached in 3 min upon MW heating. These results clearly demonstrated that even small amounts of IL were able to change the dielectric properties of a less polar solvent. These changes are sufficiently significant to heat more rapidly the reaction medium and to reach higher reaction temperatures. Increasing the amount of IL to 0.075 mmol led to a more rapid heating of the reaction mixture, as expected. When 0.150 mmol concentration was used, it provided a profile that allowed heating the DCE doped with IL to 190 °C in 1 min. To minimize the risk of potential contaminations or side reactions caused by the IL, all the following cycloaddition studies were carried out using this set of conditions (0.150 mmol IL for 2 mL of DCE) in 100 mg of 2(1*H*)-pyrazinones to obtain the chloro-bicycles. After, the hydrolysis reaction was carried out to obtain the dione-bicycles with yields of 57-77%.

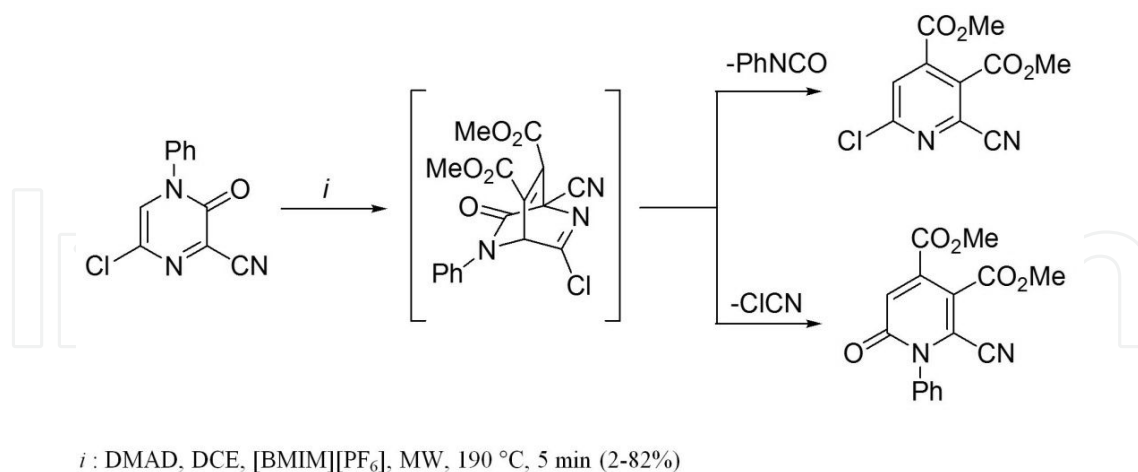
The same authors [56] reported the synthesis of the chloro-pyridine and pyridone from the cycloaddition reaction of 2(1*H*)-pyrazinone with dimethylacetylenedicarboxylate (DMAD) under the MW/IL conditions (Scheme 5). The reactants 2(1*H*)-pyrazinone and DMAD were used in a molar ratio of 1:1. The reaction conditions used were the same reported previously, 190 °C, DCE/[BMIM][PF₆] (0.150 mmol IL for 2 mL of DCE) in 5 min to furnish yields of

82% of chloro-pyridine and 2% of pyridine. Another cycloaddition reaction used heterodienes with ethene, leading to the bicyclic cycloadducts was investigated by these authors. However, using IL as a doping agent in the DCE was not successful because this reaction was not suitable for MW irradiation.



Scheme 4.

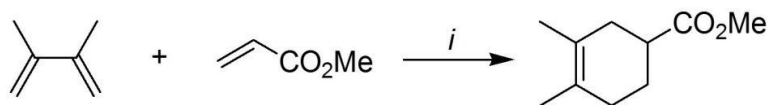
Leadbeater and Torenus [53] described the Diels-Alder reaction from equimolar amounts of 2,3-dimethylbutadiene and methyl acrylate to furnish the [4 + 2] adduct cyclohex-3-ene using a mixture of TOL (2 mL) and [*i*PrMIM][PF₆] (55 mg) under MW irradiation (Scheme 6). The mixture was irradiated at 200 °C for 5 min and led to the cyclohex-3-ene in 80% yield. The power used during the reaction performed under MW irradiation was 100 W. In a control experiment, the reaction was repeated in the absence of [*i*PrMIM][PF₆], and it was found that after the same time (5 min at 100 W power) there was no product formed.



Scheme 5.

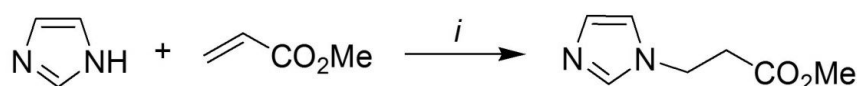
The same authors studied [53] the reaction of Michael addition from equimolar amounts of imidazole and methyl acrylate to furnish the methyl 3-(imidazol-1-yl) propionate (Scheme 7). The mixture of TOL (2 mL) and [*i*PrMIM][PF₆] (55 mg) was irradiated for 2 min (200 °C, 100 W) and led to the methyl 3-(imidazol-1-yl)propionate in 75% yield. The reaction was re-

peated firstly in the absence of IL and TOL and secondly in the absence of TOL; in both cases after the same time and power (2 min at 100 W) there was no product formed.



i: TOL, [PMIM][PF₆], MW, 100 W, 200 °C, 5 min (80%)

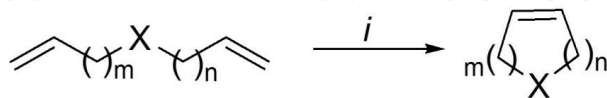
Scheme 6.



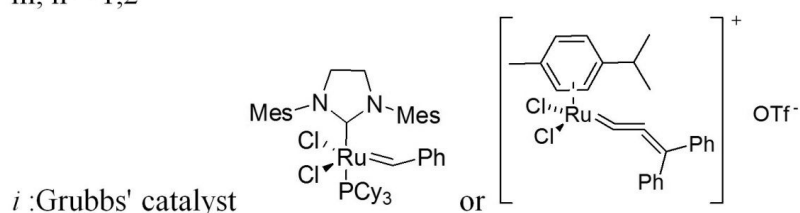
i:TOL, [PMIM][PF₆], Et₃N, MW, 100 W, 200 °C, 2 min (75%)

Scheme 7.

Garbacia *et al.* [57] described the ring-closing metathesis reactions (RCM) using diene substrates to furnish rings of five-, six-, or seven membered carbo- or heterocycles under MW irradiation (Scheme 8). The mixture of dienes (X = NTs, m,n = 1) and 0.5 mol% Grubbs' catalyst in the presence of DCM/[BMIM][PF₆] (0.04 M of IL) was irradiated in MW for 15 s, furnishing the desired product in > 98% yields. When neat DCM was used after the same time period only 57% conversion was observed. The authors mentioned that this was not a surprise since the reaction temperature during the full irradiation event (0-15 s) was significantly lower for the neat solvent. On the other hand, it was not possible to use the cationic ruthenium allenylidene catalyst in conjunction with an IL-doped solvent. With both [BMIM][PF₆] and [BMIM][BF₄] (0.04 M in DCM), conversions were below 30%, presumably due to catalyst deactivation.



X = NTs, O, CHOTs, C(CO₂Et)₂
 m, n = 1,2



Scheme 8.

Leadbeater *et al.* [54] also reported the conversion of alcohols to alkyl halides using IL. Initially, they screened a range of reaction conditions mediated by MW irradiation using 100 W of power. Focusing on 1-octanol, they varied the MW irradiation time (0.5–10 min), the ILs ([PMIM][I], [PMIM][Br], [BMIM][Cl]) and the acid (PTSA, H₂SO₄). The reaction was performed from equimolar amounts of alcohol, IL and acid. The authors also investigated the effects of the addition of TOL as co-solvent (2 mL). When these reactions were carried out with neat IL, they reached 200 °C in a few seconds (≤ 15 s). On the other hand, using TOL as co-solvent it took a little longer to heat up but still reached 200 °C within a matter of 30–40 s (Table 6). Results showed that PTSA was more efficient than H₂SO₄ in the reactions involving the iodo, bromo and chloro ILs. Reaction times were in an increasing order: iodo < bromo < chloro substitutions with 0.5, 3 and 10 min, respectively. Most of the reactions using neat ILs presented higher product yields. The use of 2 mL of TOL as a co-solvent decreased the yield of the product formed.

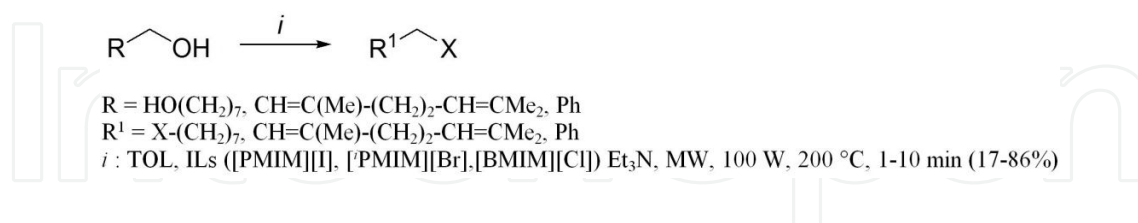
IL/(Nucleophile)	Time (min)	Acid	Product	Yield ^a (%)	Yield ^a (%)
				Without co-solvent	With co-solvent
[PMIM][I]	0.5	PTSA	CH ₃ (CH ₂) ₇ -I	81	56
[PMIM][I]	1	PTSA	CH ₃ (CH ₂) ₇ -I	53	38
[PMIM][I]	0.5	H ₂ SO ₄	CH ₃ (CH ₂) ₇ -I	3	55
[PMIM][I]	1	H ₂ SO ₄	CH ₃ (CH ₂) ₇ -I	38	15
[PMIM][Br]	0.5	PTSA	CH ₃ (CH ₂) ₇ -Br	68	42
[PMIM][Br]	3	PTSA	CH ₃ (CH ₂) ₇ -Br	95	32
[PMIM][Br]	0.5	H ₂ SO ₄	CH ₃ (CH ₂) ₇ -Br	73	59
[PMIM][Br]	1	H ₂ SO ₄	CH ₃ (CH ₂) ₇ -Br	42	40
[BMIM][Cl]	3	PTSA	CH ₃ (CH ₂) ₇ -Cl	32	0
[BMIM][Cl]	3	H ₂ SO ₄	CH ₃ (CH ₂) ₇ -Cl	49	8
[BMIM][Cl]	10	PTSA	CH ₃ (CH ₂) ₇ -Cl	42	35

^aYield of isolated product.

Table 6. Reaction conditions of 1-octanol with IL/(Nucleophile) [54].

Having found suitable conditions, the reaction was performed to a range of different alcohols. Further optimization of the reaction showed that the best reaction conditions for obtaining the 1-octanol were when IL was used in reaction medium. On the other hand, some dihalogenate 1,8-octanediol have furnished the best results when the co-solvent method was used as showed in Table 7. When using geraniol, not unexpectedly, geranyl iodide could not be isolated, but bromide and chloride could be obtained (Table 7). When using benzyl alcohol, it was possible to obtain the iodide in moderate yield (46%), the bromide in good yield

(68%) but only the chloride in low yield (17%). The authors believe that the co-solvent method is better because the organic product is more soluble in the organic solvent than in the IL and that once formed it moves to the organic layer and is protected from decomposition which can occur in the higher-temperature, acid IL environment.



Alcohol	IL	Product	Time (min)	Yield ^a (%)
1,8-Octanediol ^b	[PMIM][I]	I-(CH ₂) ₈ -I	3	53
1,8-Octanediol ^b	[PMIM][Br]	Br-(CH ₂) ₈ -Br	3	86
1,8-Octanediol ^b	[BMIM][Cl]	Cl-(CH ₂) ₈ -Cl	10	50
Geraniol	[PMIM][I]	I-CH=C(Me)-(CH ₂) ₂ -CH=CMe ₂	0.5	Dec ^c
Geraniol	[PMIM][Br]	Br-CH=C(Me)-(CH ₂) ₂ -CH=CMe ₂	3	47
Geraniol	[BMIM][Cl]	Cl-CH=C(Me)-(CH ₂) ₂ -CH=CMe ₂	10	30
Benzyl alcohol	[PMIM][I]	PhCH ₂ -I	1	46 (72) ^d
Benzyl alcohol	[PMIM][Br]	PhCH ₂ -Br	3	68
Benzyl alcohol	[BMIM][Cl]	PhCH ₂ -Cl	10	17

^aYield of isolated product. ^b0.5 mmol alcohol. ^cDec = decomposition observed. ^d3 min.

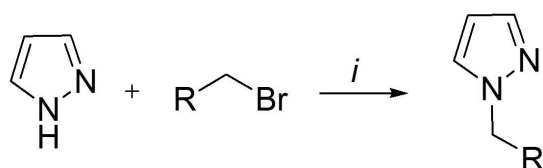
Table 7. Conversion of alcohols to alkyl halides using co-solvent method [54].

Silva *et al.* [63] used the MW irradiation technique in the Diels–Alder reaction of tetrakis(pentafluorophenyl)porphyrin with pentacene and naphthacene. One of the synthetic methods used for the synthesis of these compounds was the use of IL-doped under MW irradiation. In order to increase the product yields, the authors used NMP and DCB as solvent systems with higher loss tangents, doped with an [BMIM][PF₆]. Unfortunately, none of these experiments gave better results.

5. Ionic Liquids as Doping Agents in Microwave Assisted N-Alkylation Reactions

Reactions of *N*-alkylation of pyrazoles using IL as doping agent under MW irradiation have been little explored. Leadbeater and Torenus [53] studied the reaction of alkylation of pyra-

zoles used 1H-pyrazole and alkyl halides to furnish 1-alkylpyrazoles under MW irradiation (Scheme 9). The authors found that to this reaction the product was not obtained using 2 mL of TOL and 55 mg of [iPrMIM][PF₆], which were reaction conditions previously established for other reactions (Diels-Alder and Michael addition). Although the authors did not manage to characterize the reaction products, they affirm that *"it is clear to see that all the IL is destroyed since the biphasic starting mixture (solvent and IL) becomes a monophasic mixture after just a few seconds of MW irradiation. This shows the limitations of our protocol; it not being possible to undertake reactions which use or generate nucleophiles such as halide ions"*.



R = aryl

i: TOL, [PMIM][PF₆], Et₃N, MW, 100 W, 200 °C

Scheme 9.

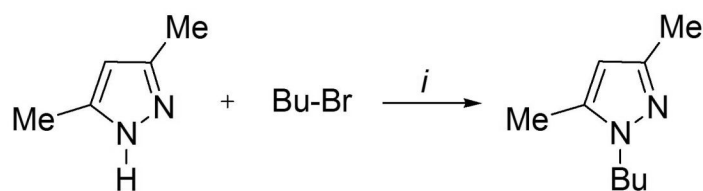
Taking into account the results found by Leadbeater and Torenus [53], Kresmsner *et al.* [51] described the use of passive heating elements (PHEs) in *N*-alkylation of pyrazoles using NH-pyrazole and 1-(2-bromoethyl) benzene to obtain 1-phenethyl-1H-pyrazole. PHEs are materials which allow the compounds with low absorption of MW irradiation or poorly absorbing solvents such as HEX, carbon tetrachloride, THF, DIO, or TOL to be effectively heated to temperatures far above their boiling points (200-250 °C) under sealed vessel MW conditions. Thus, the authors used cylinders of sintered silicon carbide (SiC), PHE, which are chemically inert and strongly MW absorbing materials in the reactions of alkylation of pyrazoles.

Based on the studies mentioned above, we decided to explore the doping capacity of IL under MW irradiation in the *N*-alkylation of pyrazoles. This is a fundamental reaction of broad synthetic utility that often requires basic catalysis and thermodynamic reaction conditions. In addition, *N*-alkylation reaction of this heterocycle is a synthetic approach useful in the preparation of building blocks for the synthesis of important active compounds like pharmaceuticals [64] and agrochemicals [65]. In this way, it is clear the importance to develop a new methodology regarding this reaction. Our research group has previously reported the *N*-alkylation of pyrazoles using IL as solvent in oil bath [31]. Thus, we focused the use of efficient MW irradiation to perform the *N*-alkylation of pyrazoles in less polar solvents. Since these molecular solvents poorly absorb MW irradiation due to their lower loss tangent, the use of IL as doping agents becomes essential to achieve high temperatures. A symmetrical pyrazole and two reactive alkyl halides were chosen to perform these tests. [BMIM][BF₄] was selected due to its successful results in our previous work of *N*-alkylation in oil bath [31]. The amount of IL employed was ~ 0.1 mmol.mL⁻¹, which represents the minimum quantity required to achieve 150 °C in the four solvents under

study – HEX, TOL, THF and DIO (Figure 3) [66]. We also selected a base, KOH, to investigate the influence of basic catalysis on this reaction [31]. Initially, the reaction between butyl bromine and 3,5-dimethylpyrazole was performed in absence of basic catalysis. Based on data presented in Table 8, we could see that the reaction in HEX achieved the highest conversion followed by TOL, THF and DIO. In a basic medium, the conversion was increased only for TOL and DIO. The maintenance of moderate conversions could be explained by the low solubility of KOH in the solvents employed (Table 8).

Thus, we decided to investigate if a change in the alkylant agent reactivity could lead to higher conversions. Since iodine is a better leaving group than bromine, ethyl iodine was chosen to react with 3,5-dimethylpyrazole. Higher conversions were achieved for all tested solvents when compared with the results mentioned previously (Table 9). These results suggest that the nature of the leaving group would have greater influence than the basic catalysis on the product conversion.

Contrary to the results of Leadbeater and Torenus [53], we chose substrates for the reaction that showed moderate to good conversions. Thus, the IL is shown as an alternative to passive heating elements PHE [13].

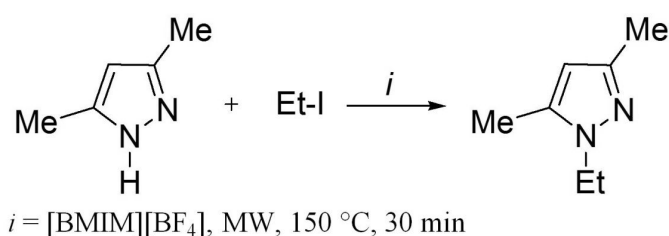


$i = [\text{BMIM}][\text{BF}_4]$, MW, 150 °C, 30 min

Entry	Solvent ^a	Base	$[\text{BMIM}][\text{BF}_4]$ (mmol.mL ⁻¹)	Conversion (%) ^b
1	HEX	-	0.117	59
2	HEX	KOH	0.123	50
3	TOL	-	0.123	17
4	TOL	KOH	0.127	37
5	THF	-	0.113	17
6	THF	KOH	0.124	17
7	DIO	-	0.108	9
8	DIO	KOH	0.118	41

^a3mL. ^bDetermined by ¹H NMR.

Table 8. Conversion of 1*H*-pyrazole in 1-butylpyrazole in low polar solvents in presence of $[\text{BMIM}][\text{BF}_4]$.



Entry	Solvent ^a	[BMIM][BF ₄] (mmol.mL ⁻¹)	Conversion (%) ^b
1	HEX	0.123	75
2	TOL	0.114	43
3	THF	0.120	71
4	DIO	0.118	43

^a3mL. ^bDetermined by ¹H NMR.

Table 9. Conversion of 1*H*-pyrazole in 1-ethylpyrazole in low polar solvents in presence of [BMIM][BF₄].

6. Conclusions

After analysis of the literature and results previously obtained by us about ILs as doping agents under MW irradiation, it is possible to conclude that: (i) the use of a small amount of IL in less polar solvents such as THF, TOL, and HEX promotes efficient heating under MW irradiation in sealed vessels; (ii) solvents with low $\tan \delta$ when doped with small amounts of ILs are generally ideal reaction media as they allow a very rapid heating by MW irradiation in sealed vessels; (iii) an important limitation in the use of ILs as a doping agent is the chance of IL decomposition at temperatures higher than its thermal stability.

The examples of ILs as doping agents reviewed in this chapter showed that their applications are little explored and they have the potential to become an area of greater interest in the organic synthesis.

7. List of Abbreviations

ACN	Acetonitrile
[BMIM][BF ₄]	1-Butyl-3-methylimidazolium tetrafluoroborate
[BMIM][Br]	1-Butyl-3-methylimidazolium bromide

[BMIM][I]	1-Butyl-3-methylimidazolium iodide
[BMIM][PF ₆]	1-Butyl-3-methylimidazolium hexafluorophosphate
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIO	Dioxane
DMF	N,N-Dimethylformamide
DMAD	Dimethylacetalenedicarboxylate
[DMMBisIM][I]	(Bis(1-methylimidazol-3-yl))methane iodide
[DMMBisIM][PF ₆]	(Bis(1-methylimidazol-3-yl))methane hexafluorophosphate
[EMIM][Tf ₂ N]	1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide
Grubbs' catalyst	Grubbs' Catalysts (are a series of transition metal carbene complexes used as catalysts for olefin metathesis)
[HBIM][BF ₄]	1-Buthylimidazolium tetrafluoroborate
[HBIM][PF ₆]	1-Buthylimidazolium hexafluorophosphate
[HBIM][Tf ₂ N]	1-Buthylimidazolium bis(trifluoromethylsulfonyl)amide
HEX	Hexane
[HEIM][Tf ₂ N]	1-Ethylimidazolium bis(trifluoromethylsulfonyl)amide
[HMIM][Tf ₂ N]	1-Methylimidazolium bis(trifluoromethylsulfonyl)amide
ILDA	Ionic Liquids as Doping Agents
[ⁱ PMIM][Br]	1- <i>iso</i> -Propyl-3-methylimidazolium bromide
[ⁱ PMIM][PF ₆]	1- <i>iso</i> -Propyl-3-methylimidazolium hexafluorophosphate
[PMIM][I]	1-Propyl-3-methylimidazolium iodide
PTSA	<i>p</i> -Toluenesulfonicacid
PHEs	Passive Heating Elements
RCM	Ring-Closing Metathesis
TOL	Toluene
THF	Tetrahydrofurane

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Author details

Marcos A. P. Martins*, Jefferson Trindade Filho, Guilherme S. Caleffi, Lilian Buriol and Clarissa P. Frizzo

*Address all correspondence to: mmartins@base.ufsm.br

Department of Chemistry, NUQUIMHE, Federal University of Santa Maria, Brazil

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- [62] The experiments were performed in a Discover CEM MW using the mode of operation: with simultaneous cooling and temperature sensor fiber optics. The power of

the equipment was established at 200 W (or 300 W when necessary). A microwave vessel (10 mL) equipped with a standard cap (vessel commercially furnished by Discover CEM) was filled with solvent (3 mL) and [BMIM][BF₄] (quantities indicated in Table 5). After the vessel was sealed, the sample was irradiated for 5 min at 150 °C, which was plotted in Synergies Version 3.5.9 software and a maximum level of internal vessel pressure of 250 psi. The irradiation powers are indicated in Table 5. The solvents doped were subsequently cooled to 50 °C by compressed air.

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- [66] The experiments were performed in a Discover CEM MW using the mode of operation: with temperature sensor fiber optics; without simultaneous cooling. The power of the equipment was established at 200 W. A microwave vessel (10 mL) equipped with a standard cap (vessel commercially furnished by Discover CEM) was filled with 1 mmol of 3,5-dimethylpyrazole and 1.2 mmol of 1-bromobutane or iodoethane besides the addition of ~ 0.1 mmol.mL of [BMIM][BF₄] (quantities indicated on Tables 8 and 9) and 3 mL of solvent (Tables 8 and 9). KOH was also added in equimolar amount to 3,5-dimethylpyrazole (1 mmol) at experiments indicated in Table 8. The vessel was sealed. The sample was irradiated for 30 min at 150 °C under high stirring and a maximum level of internal vessel pressure of 250 psi. The solvent of the resultant mixture was evaporated under reduced pressure. After this step, the conversion was determined by ¹H NMR. The ¹H NMR spectra were recorded on a Bruker DPX 400 (¹H at 400.13 MHz) and in CDCl₃/TMS solutions at 298 K. The spectroscopy data for compounds 1-butyl-3,5-dimethyl-1*H*-pyrazole and 1-ethyl-3,5-dimethyl-1*H*-pyrazole are present in the references: [31] and Potapov A. S., Khlebnikov A. I., Ogorodnikov V. D. (2006). Synthesis of 1-Ethylpyrazole-4-carbaldehydes, 1,1'-Methylenebis(3,5-dimethylpyrazole-4-carbaldehyde), and Schiff Bases Derived Therefrom. *Russian Journal of Organic Chemistry*, 42(4), 550-554, respectively.

