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## Sonochemical Heating Profile for Solvents and Ionic Liquid Doped Solvents, and Their Application in the *N*-alkylation of Pyrazoles

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## Abstract

The heating profile for 25 solvents was determined in ultrasonic probe equipment at amplitudes of 20, 25, and 30 %. Each solvent was heated in accordance with its boiling point. The effect of vapor pressure, surface tension, and viscosity of the solvents in dissipated ultrasonic power (Up) was evaluated. Multiple regression analysis of these solvent properties and dissipated Up reveals that solvent viscosity is the property that most strongly affected dissipated Up. Experimentation involving acetonitrile doped with [BMIM][BF<sub>4</sub>] indicated faster heating than MeCN. Aprotic polar solvents such as DMSO, DMF, and MeCN were tested in the *N*-alkylation of pyrazoles under ultrasonic conditions. After 5 min at 90 °C, the reactants had been totally converted into product in these solvents. Solvents, with low dissipated Up (e.g., toluene) were tested. Conversions were lower compared to those of aprotic polar solvents. When the reactions were done in hexane, no conversion to product was observed. To check the effect of doping in solvents with low Up, [BMIM][BF4], DMSO, and DMF were selected. The conversions for toluene doped with [BMIM][BF4], DMSO, and DMF were selected. The conversions were greater than when done in just toluene (46 %). Thus, [BMIM][BF4] was the best polar doping solvent, followed by DMSO. DMF was not considered to be a satisfactory doping solvent. No conversion was observed for reactions in the absence of base performed in DMSO, DMF, and MeCN doped with [BMIM][BF4].

## **Graphical abstract**



Keywords Dissipated Ultrasonic Power, Ionic Liquid Doped Solvents, N-alkylation reaction.

#### 1. Introduction

Ultrasonic irradiation is widely used in chemistry, and its applications extend to various areas, including organic and organometallic chemistry, materials science, aerogels, food chemistry, and medicinal research [1,2]. The use of ultrasound to promote chemical reactions is called sonochemistry, and it has become an exciting field of research during recent years because the chemical effects of ultrasound are diverse and lead to substantial improvements in chemical reactions. Ultrasonic probe equipment has shown many advantages over ultrasonic cleaning baths. It allows programming of various parameters like amplitude, pulse, and monitoring the rise in temperature with time. Such control is important for ensuring the reproducibility and reliability of the method. Additionally, recent publications have shown high yields obtained in shorter reaction times when compared to conventional methods [1–6].

The effects of ultrasonic irradiation on the physical properties of the medium can decisively affect chemical reactivity [7]. The most common effects are related to heating, cavitation, shaking, acoustic transmission, instability at the interface friction, diffusion, and mechanical disruption. However, the cavitation effect is considered to be the most important one. This phenomenon is a physical process that leads to the formation of cavities or gaseous vapor cavities inside the irradiated liquid, which are created, grow, and subsequently implode. The great importance of this phenomenon is associated with the bubbles (cavities) formed, since they provide very high local temperatures and pressures, which leads to a turbulent flow of the fluid and subsequent increase in mass transfer [8,9].

The cavitation intensity is obviously linked to dissipated power, and any increase in dissipated power that enters into a reaction system will be associated with an increase in cavitation effect [7,10]. Despite the liquid properties that influence cavitation, sonochemical literature has little to say about parameters that influence dissipated power, particularly for non-aqueous systems [11]. On the other hand, it is very difficult to explain the energy dissipation in organic solvents by looking at a particular physical property, but it is possible to note that dissipated ultrasonic power (Up) decreases for solvents with high volatility [11]. Additionally, the power dissipated by the ultrasonic wave into the bulk medium is a key parameter required to express the efficiency of a sonochemical [12,13].

Due to these advantages, ultrasound has been utilized by our research group to promote the synthesis of different compounds like isoxazoles [3], pyrazoles [4], *N*-propargylic ß-enaminones [14], pyrazolo[1,5-*a*]pyrimidines [5], and 1,2,4-triazolo [1,5-*a*]pyrimidines [6]. The N-alkylation of heterocycles has been reported as a key route to prepare biological active compounds. Despite the importance and the limitations related with N-alkylation reaction, this reaction is underexplored in sonochemsitry [15-18]. Thus, the ultrasound method has proven to be an effective and highly attractive methodology, due to advantages such as it being a simple procedure with easy work-up, short reactions times, mild conditions, and excellent yields. On the other hand, in a search through the literature, any relate was found for influence of the thermal profile of solvents or doped solvents on the progress of the reactions under ultrasound irradiation.

Based on these facts, the aim of this work is: firstly, to report the results obtained from a systematic study of the effects caused on the heating ramp by ultrasonic irradiation in different solvents and ionic liquid doped solvents; and also to evaluate the effect of amplitude, vapor pressure, viscosity, surface tension, and temperatures reached in the dissipated Up. Subsequently, the *N*-alkylation reaction of 3,5-dimethyl-*1H*-pyrazole with 1-bromobutane [19] was evaluated in order to evaluate the ramped solvents in an organic reaction. Then, the scope of *N*-alkylation was investigated for other pyrazoles and alkylants agents.

## 2. Materials and methods

**2.1 Equipment**: The ultrasound experiments were done with a tapered microtip probe (6 mm) connected to a Sonics Vibra-Cell<sup>TM</sup> (500 W) ultrasonic processor equipped with an integrated temperature control probe. The heating ramps were performed for different pure solvents, using ultrasound equipment and operating with a probe of 6 mm. The device operates at 20 kHz of frequency and the amplitude was set to 20 % of the maximum power output. The equipment can operate at a maximum temperature of 99 °C. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance III 600MHz Bruker Avance III (<sup>1</sup>H at 600 MHz and <sup>13</sup>C at 150 MHz) in CDCl<sub>3</sub>/TMS solutions at 298 K. The general reproducibility of chemical shift data was estimated to be not greater than  $\pm$  0.01 ppm. All spectra were acquired in a 5 mm tube, at natural abundance. Chemical shifts are given in ppm. GC-Mass Spectroscopy (GC-MS) analyses were performed on a Agilent 5975B El/CI – MSD system operating in the EI mode at 70 eV, equipped with a split/splitless injector (250°C) cross-linked to a HP-5 capillary column (30 m, 0.32 mm i.d.), and helium was used as the carrier gas. The transfer line temperature was 280°C.

**2.2 Solvents and reactants:** The solvents selected for this study include dichloromethane, acetone, chloroform, methanol, tetrahydrofuran, hexane, diethylacetate, ethanol, benzene, cyclohexane, acetonitrile, 1-propanol, water, toluene, 1-butanol, acetic acid, 1-octanol, dimethylformamide, cycloexanone, bromobenzene, 1,2-dichlorobenzene, dimethylsulfoxide, benzonitrile, and nitrobenzene. All solvents were used, unless indicated otherwise, without prior purification. Ionic liquid [BMIM][BF<sub>4</sub>] is comercially available and [OMIM][BF<sub>4</sub>], [BMIM][OH], [DBMIM][BF<sub>4</sub>], and [Bpy][OH] had been synthesized by our research group according to procedures already extensively described in the literature [20].

**2.3 Ramp heating for neat solvents**: A vessel of 5mL and a tip of 6 mm were used in all experiments. The programmed amplitudes were 20, 25 and 30 %, and a continuous pulse was kept. Temperature was set in accordance with the boiling point of the solvent group. Solvents from groups 1 and 2 were heated to 70 °C, while solvents from group 3 were heated to 99 °C. Ninety seconds was enough time to observe the maximum elevation of temperature during irradiation. For doped solvents, 1.5 mmol of ionic liquid was used.

**2.4** *N*-alkylation reaction: In a 5 mL vessel with 0.096 g (1 mmol) of the 3,5-dimethyl-1*H*-pyrazole and 0.056 g (1 mmol) of KOH, 5 ml of solvent and 0.16 g (1.2 mmol) of the butyl bromide were added, respectively. The reaction was performed at 90 °C, for 5 or 10 min of irradiation. A 5mL vessel and a tip of 6 mm at 25% amplitude were used in all experiments. Doping experiments were performed with 1.5 mmol of ionic liquid. After the reaction time, an aliquot was withdrawn from the mixture, which was diluted in 2 ml of acetonitrile HPLC, filtered into a vial, and submitted to mass spectrometry analysis to determine the conversion. Diethyl ether (3 mL) was added, and the resulting product was extracted from the ionic liquid. The diethyl ether was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness leaving the desired pyrazoles. When ionic liquid was retained in diether ether, water (10 ml) was added, and the resulting product was extracted with chloroform (3 × 10 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to dryness to obtain the desired products in a pure form. Compounds **3a-c**, **5a-c** and **7a-c** were characterized by spectroscopic methods. Spectral data for compounds **3a, 5a, 3c, 5c** [19] and **5b** [19b] was satisfactory in accordance with reference. Spectral data for compounds **7a, 3b, 7b** and **7c** is given bellow.

Spectral data of 1-(1-methylpropyl)-3,5-dimethyl-1*H*-pyrazole **7a**: (C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>), oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 0.77$  (t, 3H), 1.44 (d, 3H, <sup>2</sup>*J* = 6.85 Hz), 1.75 (m, 1H), 1.94 (m, 1H), 2.23 (s, 6H), 4.08 (m, 1H), 5.78 (s, 1H).

<sup>13</sup>C NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.5, 11.0, 13.0, 20.5, 29.6, 55.4, 104.6, 139.3, 146.8. GC/MS (EI, 70 eV) *m/z* 152 (M<sup>+</sup>, 61), 109 (100), 137 (19), 123 (5), 96 (65).

Spectral data of 1-butyl-1*H*-pyrazole **3b:** (C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>), oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.5$  (s, 1H); 7.37 (s, 1H), 6.23 (s, 1H), 4.14 (t, 6 Hz, 2H), 1.84 (m, 2H), 1.31 (m, 2H), 0.93 (t, 6 Hz, 3H). <sup>13</sup>C NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 138.9$ , 128.9, 105.2, 51.8, 32.5, 19.8, 13.6. GC/MS (EI, 70 eV) *m/z* 124 (M<sup>+</sup>, 22), 81 (100), 68 (26). Spectral data of 1-butyl-1-(1-methylpropyl)-1*H*-pyrazole **7b:** (C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>), oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.49$  (s, 1H), 7.37 (s, 1H), 6.21 (s, 1H), 4.23 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.47 (m, 3H), 0.78 (m, 3H). <sup>13</sup>C NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 138.6$ , 127.1, 104.7, 59.6, 30.2, 20.9, 10.6. GC/MS (EI, 70 eV) *m/z* 124 (M<sup>+</sup>, 30), 95 (100), 68 (86)

Spectral data of 1-(1-methylpropyl)-5-trifluoromethyl-3-Methyl-1*H*-pyrazole **7c:** ( $C_9H_{13}F_3N_2$ ), oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 6.31$  (s, 1H), 4.23 (m, 1H), 2.36 (s, 3H), 2.07 (m, 1H), 1.90 (m, 1H), 1.57 (d, 7Hz, 3H), 0.66 (m, 3H).<sup>13</sup>C NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 140.9$ , 143.2 (q, 38Hz), 120.9 (q, 268 Hz), 105.7, 58.1, 30.3, 21.3, 13.5, 10.6. GC/MS (EI, 70 eV) *m/z* 206 (M<sup>+</sup>), 150 (100), 131 (23), 81 (17).

Spectral data of 1-(1-methylpropyl)-3-trifluoromethyl-5-methyl-1*H*-pyrazole **7c**<sup>2</sup>:  $C_9H_{16}N_2$ ), oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 6.23$  (s, 1H), 4.16 (m, 1H), 2.29 (s, 3H), 1.99 (m, 1H), 1.78 (m, 1H), 1.46 (d, 7Hz, 3H), 0.77 (t, 7 Hz, 3H).<sup>13</sup>C NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 140.9$ , 143.2 (q, 38Hz), 120.9 (q, 268 Hz), 105.7, 58.1, 30.3, 21.3, 13.5, 10.6. GC/MS (EI, 70 eV) *m/z* 206(M<sup>+</sup>, 38), 191 (23), 163 (89), 149 (31), 137 (1.5) 108 (3).

**2.5 Dissipated ultrasonic power (Up):** The acoustic pressure can be determined using a calibrated hydrophone (acoustic method). The Up was determined by the calorimetric method. In this method, cell sonication acts as a calorimeter, containing a volume, V, of liquid irradiated for a period of time, dt. The mechanical energy is converted into heat, and the temperature increase, dT, is measured and plotted on a graph as a function of dt. In the linear part of the graph, the slope dT/dt is deduced, and this data is inserted into the following equation:

 $U_p(W) = C_p M(dT/dt);$ 

in which  $C_p$  is the heat capacity of the solvent at constant pressure (J kg<sup>-1</sup> K<sup>-1</sup>), M is the mass of the solvent (kg), and dT/dt is the increase in temperature per second [20].

## 3. Results and Discussion

Solvents were selected and classified in groups according to boiling points. Group 1 included dichloromethane, acetone, chloroform, methanol, THF, and hexane; group 2 included diethylacetate, ethanol, benzene, cycloexane, acetonitrile, 1-propanol, and water; while group 3 included toluene, 1-butanol, acetic acid, 1-octanol, DMF, cycloexanone, bromobenzene, 1,2-dichlorobenzene, DMSO, benzonitrile, nitrobenzene, and [BMIM][BF4]. Initially, the temperature was programmed into the equipment according to the boiling points of the solvent to be analyzed, and then irradiation remained continuous. In group 1 and 2, the programmed temperature was 70 °C; while for solvents of group 3, the programmed temperature was 99 °C. In order to build the heating ramps for each solvent, a volume of 5mL was irradiated at amplitude rates of 20, 25, and 30%, which corresponds to 41, 51, and  $61\mu$ m for a 6 mm probe. All experiments were done over a period of 90 s, and the temperature was verified every 15s. The initial temperature was 25 °C. The heating ramps enable the construction of a T (°C) versus t(s) graph (see **Figure 1**). The *d*T/*d*t was deduced from the linear part of the graph. At 25 %, the *d*T/*d*t ratio was slightly greater for most solvents. Chloroform showed better linearity and a higher *d*T/*d*t ratio at 20 %



amplitude; while hexane, 1-propanol, water, cyclohexane, 1-butanol, acetic acid, benzonitrile, DMF, cyclohexanone, and  $[BMIM][BF_4]$  had higher dT/dt ratios at 30 % amplitude.

**Figure 1.** The heating ramps enable the construction of graphs of  $T(^{\circ}C)$  versus t (s) for three groups of solvents at 25 % amplitude: (a) group 1; (b) group 2; and (c) group 3.

It can be seen that [BMIM][BF<sub>4</sub>] was most able to reach higher temperatures faster, followed by benzonitrile, ciclohexanone, DMSO, and 1,2-diclorobenzene. Greater differences (standard deviation) in dT/dt values were observed for these same solvents with an increase in amplitude. The dT/dt ratio was used to calculate the dissipated Up for each solvent, at all of the amplitudes evaluated. For all solvents, dissipated Up increased when the amplitude was raised from 20 to 25 % (except for chloroform which remained practically the same). For the solvents hexane, cyclohexane, 1-propanol, water, 1-butanol, acetic acid, DMF, cycloexanone, benzonitrile and [BMIM][BF<sub>4</sub>], when the amplitude was increased to 30%, the dissipated Up was greater than the value calculated for 25 % amplitude. Results show that there is little variation in dT/dt with the increase in amplitude; thus average dT/dt values and correlation coefficients (R<sup>2</sup>) are expressed in **Table 1**.

Solvent	dT/dt	R <sup>2</sup>	Solvent	dT/dt	R <sup>2</sup>
	Average (± SD) <sup>a</sup>			Average (± SD) <sup>a</sup>	
$CH_2Cl_2$	0.18 (0.01)	0.959	MeOH	0.29 (0.031)	0.971
Acetone	0.23 (0.02)	0.963	THF	0.28 (0.01)	0.974
CHCl <sub>3</sub>	0.27 (0.02)	0.988	Hexane	0.33 (0.050)	0.968
Diethylacetate	0.32 (0.04)	0.985	MeCN	0.39 (0.054)	0.982
Ethanol	0.36 (0.06)	0.990	1-propanol	0.42 (0.063)	0.993
Benzene	0.38 (0.04)	0.979	Water	0.30 (0.071)	0.993
Ciclohexene	0.37 (0.03)	0.976	Bromobenzene	0.44 (0.06)	0.991
Toluene	0.39 (0.08)	0.993	1,2-dichlorobenzene	0.50 (0.069)	0.991
Acetic acid	0.48 (0.06)	0.991	DMSO	0.51 (0.07)	0.991
1-octanol	0.44 (0.09)	0.993	Benzonitrile	0.56 (0.12)	0.992
DMF	0.45 (0.07)	0.992	Nitrobenzene	0.45 (0.06)	0.991
Cyclohexanone	0.56 (0.13)	0.992	[BMIM][BF <sub>4</sub> ]	0.80 (0.16)	0.994

**Table 1.** Average of the dT/dt values and the correlation coefficient ( $R^2$ ) for all of the solvents studied.

<sup>a</sup> dT/dt average at 20, 25, and 30 % amplitude.

Dissipated Up for all the solvents, at the amplitudes investigated, is depicted in **Figure 2**. The mass of the solvents used and the Cp of each solvent used in the calculation of the Up are given in **Table S1** in the **Supporting Data**, together with the average dissipated Up for each solvent.

The relationship of vapor pressure in the dissipation of ultrasonic energy is clearly observed. Among the solvents of groups 2 and 3, particularly for those that have lower vapor pressure, the dissipated Up values were the highest among the solvents examined. For the group 1 solvents, which have higher vapor pressures, the dissipated Up values were lower. These observations are consistent with hot-spots theory; in which cavity formation is favored in solvents with lower vapor pressures; that is, those that are less volatile [1]. The collapse of these bubbles generates a large release of energy, so the maximum temperature reached is high. The increase in vapor pressure associated with heating the liquid has as a direct consequence the reduction in the effects provided by the cavitation collapse. Therefore, in order to obtain maximum benefit in energy, any experiment should be conducted at a temperature that is as low as possible, or in a solvent with low vapor pressure; however, the results showed that for solvents with low vapor pressure, the increase in temperature does not reduce the effects caused by cavitation.



Figure 2. Dissipated ultrasonic power for each solvent at amplitudes of 20, 25, and 30 %.

In accordance with ultrasound theories, dissipated Up is related to cavitation; hence the efficiency of bubble collapses. However, it is known that solvent properties can affect the efficiency of bubble collapses during the cavitation process. Among these properties we can mention the vapor pressure, viscosity, and surface tension. A plot of Up with each of the properties was constructed, based on the solvent properties shown in **Table S1** of the **Supporting Data**.

As already observed in **Figure 2**, there is a vapor pressure relationship in the dissipation of ultrasonic energy. Among the solvents examined, dissipated Up values were highest for solvents with lower vapor pressures. Solvents with the lowest vapor pressure and very high Up values — for example, cyclohexanone, bromobenzene, 1,2-dichlorobenzene, nitrobenzene, DMSO, and [BMIM][BF<sub>4</sub>] (within the red circle in **Figure 3a**) — can be considered to be outliers, and they are responsible for the reduced correlation coefficient value (r = 0.7).

For the occurrence of cavitation, it is necessary to have the formation of a liquid-gas interface. Therefore, it might be expected that the use of solvents with low surface tension would lead to efficient cavitation. In fact, this is what is observed in a quite linear way for the solvents of group 1 (**Figure 3b**). Solvents such as CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, and acetone (illustrated in red, pink and blue, respectively in **Figure 3b**), which have higher surface tension, are those with the lowest dissipated Up. In group 2, the rule is valid only for the alcohols 1-propanol and ethanol (illustrated in dark blue and light blue, respectively in **Figure 3b**). For other group members, there is an inverse relationship: the dissipated power was higher for solvents with higher surface tension. For group 3, a few solvents (e.g., 1-octanol and cyclohexanone) maintain a direct relationship between low surface tension and high dissipated power. In fact, the majority of solvents from this group have an inverse relationship to what was expected. Solvents such as [BMIM][BF<sub>4</sub>], DMSO, 1,2-dichlorobenzene, and bromobenzene (illustrated in red, light pink, light blue, and yellow, respectively, in **Figure 3b**), which have high surface tensions, also have high dissipated power. What seems to happen is that the onset of cavitation is longer for these solvents, but the energy released is much greater. Thus, for solvents with higher surface tension, cavitation begins more slowly; however, the efficiency is increased.



**Figure 3.** Correlation between Up and (a) vapor pressure (r = 0.7) and (b) Surface Tension (r = 0.7), for all the solvents evaluated.

Besides vapor pressure, another property that affects cavitation events is the viscosity. Since the viscosity changes with an increase in temperature, we decided to determine the value of viscosity at the average temperature of the heating range for each solvent. As negative pressure must overcome natural cohesive forces that act on the liquid, any increase in these forces will hinder the onset of cavitation. Theoretically, the greater the viscosity of a solvent, the greater the dissipated power in an irradiated medium. In practical terms, it was noted that the behavior follows some linearity for groups 2 and 3, and generally the more viscous solvents had higher dissipated power (see Table S1 -Supplementary Data). Furthermore, direct correlation between viscosity and Up was not observed for all solvents. As the negative pressure must overcome the natural cohesive forces acting on the liquid, any increase in these forces will hinder the onset of cavitation. Thus, the higher the viscosity of the liquid, the greater the period of time for the onset of cavitation. The linear regression performed for each solvent property that could affect the dissipated Up indicated that all these properties can affect the dissipated Up. However, from linear correlation it is not possible to evaluate which properties have a greater ability to affect the Up. Thus, all properties were easily correlated in a multiple regression analysis, thereby determining the solvent properties which have more influence on each of the solvents. The regressions were done according to the pre-established solvent groups. For groups 1, 2 and 3, the relationships led to the equations depicted in Table 2.

<b>Table 2.</b> Multiple regression analysis of the dependence	e of Uj	o, with	average	vapor	pressure	$(\mathbf{x}_1), \mathbf{su}$	rface t	ension
$(x_2)$ , and viscosity $(x_3)$ .								

I		K
1	$y = 3.97 - 0.030x_1 - 0.084x_2 + 2.000x_3$	0.96
2	$y = 1.36 - 0.017x_1 + 0.062x_2 + 0.610x_3$	0.95
3	$y = 4.16 + 0.003x_1 + 0.016x_2 + 0.009x_3$	0.64

<sup>a</sup>  $x_1$  = vapor pressure,  $x_2$  = surface tension, and  $x_3$  = viscosity.

In accordance with the multilinear regression, it was possible to see that the vapor pressure  $(x_1)$  has little effect on the Up for all of the solvent groups. The surface tension  $(x_2)$  has a slightly greater effect, followed by the viscosity. Viscosity was the physical property that most contributes to the Up through the solvents of group 1. Thus, it can be said that the less viscous solvents (group 1) were those that resulted in greater Up. On the other hand, the contribution of viscosity  $(x_3)$  to the Up was greater from lower viscosity solvents (group 1) and lesser from groups 1 and 2. Multiple regression reveals that the Up is strongly affect by the viscosity, which is contrary to the results shown by linear correlation. At the same time, vapor pressure and surface tension revealed a less significant effect than viscosity during the cavitation process.

Thus, highly viscous solvents such as  $[BMIM][BF_4]$  contributed less to the Up, despite them reaching higher temperatures faster. Solvents for use in organic reactions are expected to provide Up efficiently and quickly to reach the reaction temperature. Thus, ionic liquid doped MeCN was assayed. A volume of 5 mL of MeCN doped with 1.5 mmol of each ionic liquid tested — ([BMIM][BF\_4], [OMIM][BF\_4], [BMIM][OH], [DBMIM][BF\_4], and [Bpy][OH]) — was submitted to 240 s of heating in order to reach 70 °C at 25 % amplitude. It could be seen that all the ionic liquids tested have a similar heating profile for quickly reaching the set temperature (**Figure 4a**). Based on these results, we selected [BMIM][BF\_4] (commercially available) in order to investigate the effect of the ionic liquid concentration on the doped solution. The heating ramps of ionic liquid doped MeCN at 25 %

amplitude, doped with 1.0, 1.5, and 3.0 mmol, are shown in **Figure 4b**. The Up was not determined for ionic liquids or doped solution because  $C_p$  was not found for either [BMIM][BF<sub>4</sub>] or [OMIM][BF<sub>4</sub>]. However, it can be seen that ionic liquid doped MeCN had a heating profile with faster heating than MeCN.



**Figure 4.** (a) The heating ramps of ionic liquid doped MeCN at 25 % amplitude; and (b) The heating ramps of ionic liquid doped MeCN at 25 % amplitude, doped with 1.0, 1.5, and 3.0 mmol.

It is important to note that some operational parameters of the ultrasound equipment such as diameter of probe, kind of vessel and volum of solvent are variable. It is important to note that some operational parameters of the ultrasound equipment such as diameter of probe, kind of vessel and volum of solvent are variable. in order to test the hypothesis that small changes in these operating parameters could result in variation of the heating profile of the solvents, a serie of experiments were performed. Firstly, probes of 3mm and 6mm diameter at amplitude of 25 % were tested. MeCN, DMF, EtOH, DMSO, MeOH and 1-butanol were selected. In a fixed volume of 5 mL, all solvents reached higher temperatures when the probe with diameter of 6 mm was used (See figures S3-S8 in SI). Subsequently, experiments using a 25 mL becker rather than a vessel (specific for ultrasound equipment) were conducted. The experiments in MeCN, DMF and EtOH were performed using the probe of 6mm at amplitude 25%. In a fixed volume of 5 mL, all solvents reached higher temperatures when the vessel specific for ultrasound equipment was used (See figure S9 in SI). Finally, experiments of volume of solvent were performed. 2.5 and 5 mL of MeCN, DMF, EtOH using the probe of 3 mm were heated at amplitude 25%. Results showed that higher temperatures were reached when volume was 2.5 mL (See figure S2 in SI). The ultrasound frequency has not been explored, since equipment used presents a fixed frequency. In summary, changes in the work conditions, even small changes, result in variation of the heating profile of solvents. In this context, it is important to highlight that heating profile shown in this work for 25 solvents was stablished using operating conditions described in the experimental section.

In order to evaluate the performance of ramped solvents in a traditional organic reaction, we selected the alkylation of a 3,5-dimethylpyrazole reaction with butyl bromide, using KOH. A series of assays were done in several aprotic solvents, using a range of temperatures and reaction times. The reaction investigated is shown in **Scheme 1**.



#### Scheme 1

Experiments were initially performed in DMSO at 60 and 70 °C. The mixture was irradiated for 10 min and the conversion of the reagents in pyrazole **3a** (Scheme 1) was 100 % (**Table 3**, entries 1 and 2). Conducting the reaction at 80 and 90 °C resulted in a conversion of 82 and 92 %, respectively (**Table 3**, entries 3 and 4). In order to verify whether or not the conversion would take place in shorter times at higher temperature, the reaction was performed at 90 °C for 1, 2.5, and 5 min, which resulted in a conversion of 100 % (**Table 3**, entries 5, 6, and 7). Taking into account that the reaction needs high temperatures and takes a relatively longer amount of time, lower conversions can be attributed to a loss in alkylation from evaporation (bp.100 °C). Additionally, decomposition of the product can be overcome. TGA analysis showed (see **Supplementary Data, Figure S1**) that the decomposition temperature of pyrazole **3a** is 102 °C, and at 32 °C the first mass loss was observed. The reactions performed in DMF behaved similarly to those done in DMSO. When the reactions were performed for 10 min at a temperature of 60 °C (**Table 3**, entry 1), the conversion of the reactants to product was 64 %. When the reactions were conducted at 70, 80, and 90 °C, products were obtained at 82, 95, and 90 % conversion rate (**Table 3**, entries 2, 3, and 4). For reactions done for 1, 2.5, and 5 min (**Table 3**, entries 5, 6, and 7), product was obtained at a 100 % conversion rate.

Entry	Time (min)	Temp. (°C)		Conver	rsion (%) <sup>a</sup>	
			DMSO	DMF	MeCN	Toluene
1	10	60	100	64	93	6
2	10	70	100	82	100	22
3	10	80	82	95	100	8
4	10	90	92	90	98	15
5	5	90	100	100	100	46
6	2.5	90	100	100	90	-
7	1	$90^{\mathrm{b}}$	100	100	30	-

Table 3. Reaction conditions at 25 % amplitude in DMSO, DMF, MeCN, and Toluene (Scheme1).

<sup>a</sup>Determined by CG/MS; <sup>b</sup>Temperature reached was 54 °C in DMSO and 60°C in DMF.

When the solvent used was acetonitrile, a proportional relationship was observed between time and temperature. The conversion rate of 93 % (**Table 3**, entry 1) was reached at the lowest temperature during 10 min. The complete conversion of reactants to product was observed by increasing the reaction temperature (**Table 3**, entries 2 and 3). In order to achieve the conversion in shorter amounts of time, the reactions were conducted at 5, 2.5, and 1 min, which resulted in conversion rates of 100, 90 and 30 %, respectively (**Table 3**, entries 5,6 and 7). In order to evaluate the performance of the reaction with the combined use of ultrasound irradiation in lesser polar solvents, experiments were performed in toluene and hexane. The conversions in toluene resulted in lower values compared to those for the more polar solvents (**Table 3**, entries 1-5). When the reactions were performed in hexane at 90 °C for 1, 2.5, 5, and 10 min, no conversion to product was observed.

To check the effect of doping in solvents with low Up, [BMIM][BF<sub>4</sub>], DMSO, and DMF were selected. The reactions were performed in solvent mixtures at a ratio of 5:1 (toluene with either [BMIM][BF<sub>4</sub>] or DMSO or

DMF; or hexane with either [BMIM][BF<sub>4</sub>] or DMSO or DMF). The conversion rates for the reactions done in toluene were 100 % for [BMIM][BF<sub>4</sub>] and 59 % for DMSO — which were greater than the conversion rate obtained in the neat reaction done in neat toluene (46%) (**Table 3**, entry 5) — and 25% for DMF (**Table 4**, entries 1, 2, and 3). In hexane, the reaction resulted in conversion only when [BMIM][BF<sub>4</sub>] was used as the doping solvent. Thus, [BMIM][BF<sub>4</sub>] was the best polar doping solvent, followed by DMSO. DMF was not considered to be satisfactory as a doping solvent.

Entry	Solvent	Doping Solvent <sup>a</sup>	Time (min)	Conversion (%) <sup>b</sup>
1	Toluene	[BMIM][BF <sub>4</sub> ]	5	100
2	Toluene	DMSO	5	59
3	Toluene	DMF	5	25
<b>4</b> <sup>c</sup>	Hexane	[BMIM][BF <sub>4</sub> ]	10	61

Table 4. Doping effect of polar solvents in toluene and hexane at 25 % amplitude (Scheme 1).

<sup>a</sup>1.5 mmol of [BMIM][BF4], 90 °C, 25 % amplitude. <sup>b</sup> Determined by CG/MS.<sup>c</sup> Temperature reached was 58 °C.

The addition of  $[BMIM][BF_4]$  could lead to an improvement in the performance of the reaction, leading to products at high conversion rates at lower temperatures. Thus, a high concentration (3.0 mmol) of  $[BMIM][BF_4]$  was tested in MeCN, toluene, and hexane. The reaction was performed at 90 °C and irradiated for 10, 5, 2.5, and 1 min. In MeCN, all tests resulted in 100% conversion. In toluene and hexane, the conversion rates were very low (8–12 %), which indicates that  $[BMIM][BF_4]$  is a good doping agent for toluene and hexane at low concentrations.

In order to show that doping effect of polar solvents working for alkylation of pyrazoles, we investigated the scope of the alkylation reaction of 3,5-dimethyl-1*H*-pyrazole, -1H-pyrazole and 5-trifluoromethyl-3-methyl-1*H*-pyrazoles (**1a-c**), with some alkylant agents (**2,4,6**) in toluene doped with [BMIM][BF<sub>4</sub>]. Reaction were performed using condition showed in **Table 4** (entry 1). Results are depicted in the **Table 5**.

R <sup>1</sup> N +	R-X <u>KOH, )))</u> 2,4,6	$R^{1} \xrightarrow{N}_{R}^{N} + Me \xrightarrow{N}_{R}^{N}$
1a,b,c		3a-c,5a-c,7a-c 3c', 5c', 7c'
R <sup>1</sup> = Me ( <b>a</b> )	R = Bu, X = Br ( <b>2</b> )	R = Bu, R <sup>1</sup> = Me ( <b>3a</b> ), R <sup>1</sup> = H ( <b>3b</b> ), R <sup>1</sup> = CF <sub>3</sub> ( <b>3</b> c)
R <sup>1</sup> = H ( <b>b</b> )	R = Bn, X = Cl ( <b>4</b> )	R = Bn, R <sup>1</sup> = Me ( <b>5a</b> ), R <sup>1</sup> = H ( <b>5b</b> ), R <sup>1</sup> = CF <sub>3</sub> ( <b>5</b> c)
R <sup>1</sup> = CF <sub>3</sub> ( <b>c</b> )	R = sec-Bu, X = Br ( <b>6</b> )	R = sec-Bu, R <sup>1</sup> = Me (7a), R <sup>1</sup> = H (7b), R <sup>1</sup> = CF <sub>3</sub> (7c)

fable 5	5. (	Conversion of	products <b>3a-c</b> , <b>5a-c</b> an	nd 7a-c for reaction	performed in toluene with	[BMIM][BF <sub>4</sub> ] <sup>a</sup>
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Entry	Pyrazole	Alkylant agent	<b>Product</b> (ratio)	Conversion (%) <sup>b</sup>	Yield(%) <sup>c</sup>
1	1a	2	<b>3</b> a	100	55
2	<b>1</b> a	4	5a	82	40
3	<b>1</b> a	6	7a	4	d
4	1b	2	3b	100	54
5	1b	4	5b	100	50
6	1b	6	7b	100	45
7	1c	2	3c+3c'(1:2)	86	45
8	1c	4	<b>5b +5c'</b> (1:5)	67	d_
9	1c	6	7c + 7c' (1:6)	28	d_

<sup>a</sup>1.5 mmol of [BMIM][BF<sub>4</sub>], 90 °C, 5 min, 25 % amplitude. <sup>b</sup> Determined by CG/MS. <sup>c</sup>Isolated Product. <sup>d</sup> Yield of isolated product was determined when conversion was higher than 80%.

The doping effect observed in toluene with  $[BMIM][BF_4]$  working well for all alkylation of pyrazoles tested. Nonsubstituted 1*H*-pyrazole (**1b**) showed conversion 100% in reaction with all alkylant agents. Probably, the absence of steric hindrance of pyrazole is main factor to explain this conversion. 1*H*-pyrazole **1b** is sterically less hindered than 1,3-dimethyl-1*H*-pyrazole (**1a**) and 5-trifluoromethyl-3-methyl-1*H*-pyrazoles (**1c**). Pyrazole **1a** showed some steric hindrance in the reaction with benzyl chloride and higher steric hindrance in the reaction with 2-butane bromide (that is a secundary alkylant agent). Pyrazole **1c**, in turn showed some steric hindrance in the reaction with butyl bromide, benzyl chloride and higher steric hindrance in the reaction with 2-butane bromide, showing that trifluoromethyl group has steric hindrance greater than methyl. All these results were expected considering a S<sub>N</sub>2 reaction that is sensitive to steric hindrance of reactants showing that studied parameters in ultrasound irradiation conditions well for all alkylation of pyrazoles. Despite of higher or total conversion, the yield of isolated product was only moderated. In general, the solubility of products and of the ionic liquid in organic solvents for extraction was similar and probably some product was lost during isolation of the pure products.

Alkylation of pyrazole **1c** also allowed to us to investigate the effect of doping effect and parameters of ultrasound in the possible isomerisation of alkylated pyrazole. It can see that 1,3-*isomer* was formed preferentially in relation 1,5-*isomer* for reaction of all alkylant agents with pyrazole **1c**. These results are in accordance with previous results related in literature for N-alkylation of pyrazole **1c** in presence of [BMIM][BF<sub>4</sub>] under conventional thermal heating [19]. Thus, we can conclude that ultrasound irradiation and doping effect did not affect the regiochemsitry of isomerisation in alkylated pyrazole (N-alkylation reaction).

Finally, aiming to evaluate the influence of base on the conversion of reactants into products in DMSO, DMF, and MeCN, a reaction was performed in the absence of KOH. Results showed that the conversion was null for all the doped solvents tested. Thus, the experiments were performed in the absence of base, in DMSO, DMF, and MeCN doped with  $[BMIM][BF_4]$ . Products were obtained at a conversion rate of 9 and 11 % for the reactions performed in DMSO and DMF, respectively (**Table 6**, entries 1 and 2). Reactions in doped acetonitrile showed no conversion (**Table 6**, entry 3). The results reveal that fast heating promoted by  $[BMIM][BF_4]$  doped solvent is not efficient for converting reactant into product in the absence of base, indicating that the effect of base is essential for the formation of product.

Table 6	. Reaction	condition	tested in	[BMIM][BF <sub>4</sub> ]	in the absence	of KOH, a	t 25 % amplitude.	(Scheme1)
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Entry	Solvent <sup>a</sup>	Conversion (%)
1	DMSO	9
2	DMF	11
3	MeCN	-b

<sup>a</sup>Doped with 1.5 mmol of [BMIM][BF<sub>4</sub>] at 90 °C, irradiated for 10 min at 25 % amplitude.

<sup>b</sup> No conversion

## 4. Conclusion

The heating profile for 25 solvents was determined in ultrasonic probe equipment at amplitudes of 20, 25, and 30 %. [BMIM][BF<sub>4</sub>] had the highest heating efficiency. Multiple regression analysis revealed that solvent viscosity affected dissipated Up more than surface tension and vapor pressure. Results showed that the higher heating

efficiency of  $[BMIM][BF_4]$  can be combined with solvents with low viscosity and low dissipated Up to increase the heating profile and efficiency of organic reactions such as *N*-alkylation of pyrazoles (S<sub>N</sub>2).

Thus, it was shown that by using organic non-polar solvents doped with  $[BMIM][BF_4]$ , we can perform *N*-alkylation of pyrazoles that requires high temperatures (e.g.,  $S_N 2$ ) under ultrasound irradiation, and which is highly efficient and does not involve the loss of solvent by evaporation and/or decomposition of product.

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## **Supplementary Data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxxx.

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- \* The dissipated ultrasonic power of 25 solvents was determinate.
- \* [BMIM][BF<sub>4</sub>] and water had the highest dissipated ultrasonic power.
- \* Toluene and toluene doped with  $[BMIM][BF_4]$  were evaluated in an  $S_N^2$  reaction.
- \* Conversion in neat toluene was 46%.
- \* Conversions in toluene doped with [BMIM][BF<sub>4</sub>] was 100%.

