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Ionic Liquids: Applications in Heterocyclic Synthesis

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1. Introduction

Ionic liquids (ILs) have become omnipresent in the recent chemical literature; for they can be used as highly customizable solvents for almost any synthetic purpose [Wasserscheid & Welton, 2008]. Especially in the industry, their application goes beyond their use as solvents. The highly diverse properties of these materials make possible a surprising number of applications. In organic reactions, although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvent or catalysts [Wasserscheid & Welton, 2008]. It is well-known that the microenvironment generated by a solvent can change the outcome of a reaction, in terms of both equilibria and rates [Pârvulescu & Hardacre, 2007]. Since ionic liquids have the potential to provide reaction media that are quite unlike any other available at room temperature, it is possible that they will dramatically affect reactions carried out in them. Undeniably, there have been many claims of great improvements in reaction yields and rates when using ionic liquids [Chiappe & Pieraccini, 2005]. Over the past decade, some authors have manifested interest in providing facts to clarify the question: "how do ionic liquids act in organic reactions?" They have found answers for particular reactions, in that ionic liquids play specific roles depending on the reaction [Martins et al., 2008]. This chapter presents some questions and the best results to afford answers about the role of ILs in the most important reactions involved in heterocyclic synthesis: cyclocondensation and 1,3-dipolar cycloaddition reactions.

Heterocycles form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often heteroaromatic derivatives. In fact, in the Comprehensive Medicinal Chemistry (CMC) database, more than 67% of the compounds listed contain heterocyclic rings [Xu & Stevenson, 2000]. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics,

reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A huge number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties [Katritzky & Rees, 1984]. It is therefore easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry.

2. Cyclocondensation reactions

Cyclocondensation (a kind of annulation reaction involving the formation of a ring from one or several acyclic precursors) is a set of condensation reactions in which one-, two-, three-, or multicomponent reactants yield a single main cyclic product with the accompanying formation of some other small molecule(s) [Müller, 1994].

2.1 Characterization of cyclocondensation reactions

Reports of the synthesis of series of three-, five-, six-, and seven-membered heterocyclic rings obtained from cyclocondensation reactions in ILs were found in the literature. These reactions were carried out with different numbers of components, as summarized in **Figure 1**. The functional groups contained in each component can react as electrophiles (E_1, E_2 and E_3) or nucleophiles (Nu_1, Nu_2 and Nu_3). In general, the electrophiles are carbon atoms present in functional groups, such as carbonyl, imine, nitrile, β-carbon of α,β-unsaturated systems, mono- and dihalo-substituted carbons, and acetal and orthoester carbons; and the nucleophiles are either carbon atoms present in the α-position of aldehydes, ketones, enols, enamines, or heteroatoms, such as nitrogen, oxygen, and sulfur.

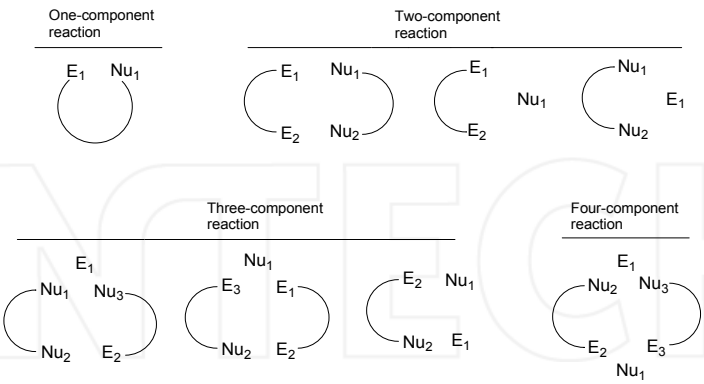


Fig. 1. Number of components in the cyclocondensation reactions in ILs found in the literature.

Table 1 shows the reaction type and building blocks that are found in cyclocondensation reactions in ILs. The first column illustrates the reaction types in accordance with the number of components. The second column explains the number of components, and the third column demonstrates the building blocks of the reactions. Thus, for example, the

representation [3 + 2] [CCC + NN] indicates that the heterocycle was formed by two building blocks, one of these building blocks possessing three atoms ([CCC]) and the other possessing two atoms ([NN]). The last column lists the heterocycles obtained. In the one-component cyclocondensation reactions, the formation of one carbon-heteroatom bond was observed. In the two-component cyclocondensation reactions either (i) the formation of two carbon-heteroatom bonds or (ii) the formation of substituted carbons or acetal and orthoester carbons was observed. The formation of carbon-carbon bonds, in general, involves a nucleophilic addition (in most cases, with a second step elimination reaction) of a carbon atom nucleophile (carbonyl α-carbon) to a carbonyl (imine or nitrile) carbon atom or to the β-carbon α,β-unsaturated systems of one carbon-heteroatom and one carbon-carbon bond. In the three-component cyclocondensation reactions there were three possibilities: (i) the formation of three carbon-heteroatom bonds, (ii) the formation of two carbon-heteroatom bonds and one carbon-carbon bond or (iii) the formation of one carbon-heteroatom bond and two carbon-carbon bonds. In the four-component cyclocondensation reactions, either (i) the formation of four carbon-heteroatom bonds or (ii) the formation of two carbon-heteroatom and two carbon-carbon bonds was observed. The formation of carbon-heteroatom bonds, in general, involves either a nucleophilic addition (in most cases, with a second step elimination reaction) of a heteroatom nucleophile (O, N, or S) to a carbonyl (imine or nitrile) carbon atom or to the β-carbon α,β-unsaturated systems or a heteroatom nucleophilic substitution into mono- and dihalo-substituted carbons or acetal and orthoester carbons.

2.2 Ionic liquids in cyclocondensation reactions

The main concern about the use of ILs in cyclocondensation reactions is the origin of catalytic effects. However, the majority of studies in the literature show that ionic liquids in cyclocondensation reactions are at a molar ratio of ≥ 1.0 in relation to substrate. With this in mind arises the question of whether they are catalysts or solvents.

Welton [Welton, 1999] has studied catalytic reactions in ionic liquids and has postulated that the potentially most powerful way in which an ionic liquid can be used in catalysis is as a combination of solvent and catalyst. From this postulate, whenever changing solvent leads to a faster reaction, the new solvent can be considered a catalyst. After all, the reaction has been accelerated, and the solvent has remained unchanged by the process. In this sense, Lee *et al.* [Lee et al., 2010] proposed some pathway to this role of ionic liquids. They suggested that ILs participate in the formation of more reactive catalytic especies, for example, in reactions catalyzed by metal triflates such as $Sc(OTf)_3$, or they stabilize intermediate reactives such as cationic vinyl, arenium intermediates and anionic oxygen radical intermediates. The authors also show the ability of ionic liquids to stabilize the transition state, for example, in the reaction of nucleophilic fluorination. Aiming to respond to the same question, Oliver-Borbigou et al. [Oliver-Borbigou et al., 2010] proposed that ILs can act as solvents and as multifunctional compounds like solvents and ligants, solvents and catalysts and stabilising agents for catalyst intermediates. From this, one might think that the function of ILs differs in different reactions or reaction condition.

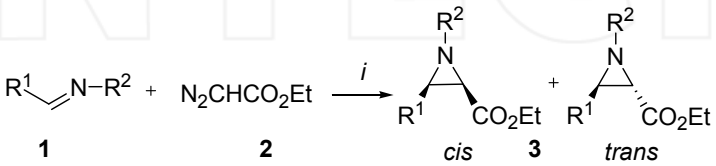
Although the solvent properties of ionic liquids are widely described, it appears that their effect is to catalyze reactions. At this point, it is worth remarking that cyclocondensation are generally not catalyzed reactions, or are acid/base catalyzed reactions. Recently, we have published a review about ionic liquids in cyclocondensation reactions to survey the most

important contributions and to discuss the role of ionic liquids in these reactions. Here, we have compiled the most important results of that work and we will briefly describe the reactions where ILs had a remarkable role.

No. Components	Reaction Type	Building Blocks	Product
One-component Reactions	[1 + 0]	[CCCCO]	Furans
	[1 + 0]	[NCNOC]	Oxadiazoles
	[1 + 0]	[CCCCCO]	Flavones
Two-component Reactions	[2 + 1]	[CN + C]	Aziridines
	[4 + 1]	[CCCC + N]	Pyrroles
	[3 + 2]	[CCO + CC]	Butenolides
	[4 + 1]	[CCCC + S]	Thiophenes
	[3 + 2]	[CCC + NN]	4,5-Dihydropyrazoles
	[4 + 1]	[NCCN + C]	Imidazoles
	[3 + 2]	[NCN + CC]	Imidazoles
	[3 + 2]	[CCC + NO]	4,5-Dihydroisoxazoles
	[4 + 1]	[NCCO + C]	Oxazoles
	[3 + 2]	[NCS + CC]	2-Thiazoles
	[5 + 1]	[CCNCS + N]	2-Thiazoles
	[4 + 1]	[NCCS + C]	2-Thiazoles
	[4 + 2]	[CCCN + CC]	Quinolines
	[3 + 3]	[CCO + CCC]	Pyrans
	[3 + 3]	[CCC + NCN]	Pyrimidinones
	[5 + 1]	[CCCCN + C]	β-Carbolines
	[5 + 1]	[NCCCO + C]	Oxazines
	[4 + 2]	[NCCS + CC]	Benzothiazines
	[4 + 2]	[NCNC + CN]	Triazines
Three-component Reactions	[2 + 3 + 1]	[CC+ NCN + C]	Pyrimidines
	[2 + 2 +1]	[CC + CO + C]	Furans
	[2 + 2 +1]	[CC + CC + S]	Thiophenes
	[2 + 2 +2]	[CC + CO + CO]	Dioxanes
	[3 + 1 + 1]	[NCN + C + C]	Imidazoles
	[3 + 1 + 1]	[CCO + C + N]	Oxazolidinone
	[3 + 1 + 1]	[CCS + C + N]	4-Thiazolidinones
	[3 + 2 + 1]	[CCN + CC + C]	Pyridines
	[3 + 2 + 1]	[CCC + CC + N]	Pyridines
	[3 + 2 + 1]	[CCN + CC + C]	Quinolines
	[3 + 2 + 1]	[CCO + CC + C]	Pyrans
	[4 + 1 + 1]	[CCCN + C + N]	Quinazolinones
	[4 + 2 + 1]	[NCCN + CC + C]	Benzodiazepines
Four-Component Reactions	[2 + 2 + 1 + 1]	[CC + CC + C + N]	Pyridines
	[2 + 1 + 1 + 1]	[CC + N + C + N]	Imidazoles
	[2 + 2 + 1 + 1]	[CC + CC + C + N]	Acridines

Table 1. Reaction types and building blocks of cyclocondensation reactions in ILs.

The first example shown here is the synthesis of aziridines **3** using ionic liquids from the reaction of imines **1** and EDA (ethyl diazoacetate) **2** (Table 2) [Xia et al., 2003]. The reaction conditions involved equimolar amounts of **1** and **2** in [BMIM][PF_6]. Under these reaction conditions, only the cis-isomer was obtained in a 93% yield. However, when a catalytic amount of [BMIM][PF_6] was used, there was no formation of aziridine **3**. These observation reported by the authors explain the results of entries **4** and **5** in Table 2, where a catalytic amount (0.1 mmol) of ionic liquid was dissolved in co-organic solvents. As summarized in Table 2, arylimines **1**, with either electron-donating or electron-withdrawing groups, reacted readily with **2** in [BMIM][PF_6], affording the corresponding aziridines **3** with high cis selectivities. The remaining ionic liquid was recovered and reused five times with only a gradual decrease in activity observed (93-91% yield). The formation of **3** in ionic liquids proceeded in a shorter reaction time, but it has been suggested to occur in a manner similar to that previously proposed for typical Lewis acids ($BF_3 \bullet OEt_2$) in molecular solvent such as hexane, in which the yield obtained was 93%, after 15 h at 25°C [Xie et al., 1999].



i: IL, r.t., 5 h.

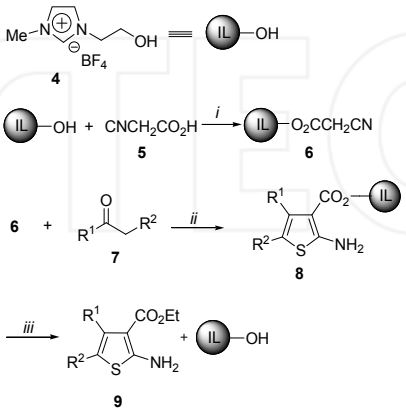
Entry[a]	IL	R^1	R^2	Product (Yield %)[b]
1	[BMIM][BF_4] [c]	Ph	Ph	82, *cis/trans*; 30:1
2	[BMIM][PF_6] [c]	Ph	Ph	95, *cis* only
3	[BMIM][PF_6]	Ph	Ph	93, *cis* only
4	[BMIM][PF_6] [d]	Ph	Ph	0
5	[BMIM][PF_6] [e]	Ph	Ph	0

[a] All reactions were carried out using 0.5 mmol of imine and 0.5 mmol of EDA in 1.5 mL of ionic liquid for 5 h. [b] The ratio of *cis* and *trans* isomers was determined by GC/MS and ^{1}H NMR. [c] 1.0 mmol of imine and 0.5 mmol of EDA. [d] 0.5 mmol of imine, 0.5 mmol of EDA and 0.1 mmol of [BMIM][PF_6] in 3 mL of CH_2Cl_2 at room temperature for 7 h. [e] 0.5 mmol of imine, 0.5 mmol of EDA and 0.1 mmol of [BMIM][PF_6] in 3 mL of hexane at room temperature for 7 h.

Table 2. Synthesis of aziridines.

The second example illustrates the role of ILs as liquid support in a cyclocondensation reaction, to synthesize 2-aminothiophenes **9** by the Gewald reaction (Scheme 1) [Hu et al., 2006]. As can be seen, the reaction of an ionic liquid with a minor excess of cyanoacetic acid (1.2 equiv) **5** in the presence of DCC (dicyclohexyl carbodiimide) and a catalytic amount of DMAP (4-dimethylaminopyridine) in dry MeCN produced the functionalized ionic liquid phase bond through ester linkage in **6**. The reactants, ketones or aldehydes **7**, S_8 and EDDA (ethylenediammonium diacetate) were then added. Finally, treatment of the corresponding products **8** with NaOEt in ethanol resulted in a very efficient cleavage of ionic liquid support to provide the 2-aminothiophenes **9** with high purity and without the need for chromatographic purification. Compared to the conventional liquid phase synthesis methods, the ionic liquid phase bond intermediates were easily isolated and purified by

simple filtration and washing with Et_2O to remove the few unreacted materials and neutral by-products. As liquid support, the ionic liquid was used at a molar ratio of 1:1 (reactant:IL). The ionic liquid phase was recovered and reused twice with no appreciable decrease in yields. The attainment of thiophenes **9** using molecular solvents such as THF entailed a painstaking and tedious procedure with the addition of $TiCl_4$ at 0°C followed by pyridine and stirring overnight at room temperature [Lütjens et al., 2003]. The yields obtained in THF/$TiCl_4$ were similar to those found in ionic liquid.

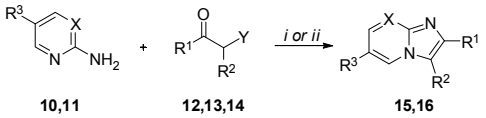


R^1 = H, Me, Et R^2 = Me, Et , CO_2Et, CO_2Me R^1, R^2 =-$(CH_2)_4$-, -$(CH_2)_3$-
i: DCC (1 equiv), DMAP (5%), MeCN, r.t., 12 h;
ii: S_8 (1 equiv), EDDA (1 equiv), 50°C, 3-6h (67-91%);
iii: EtONa (0.5 equiv), EtOH, r.t., 6 h.

Scheme 1

The reaction shown in Scheme 2 is a good example of the use of ILs as solvent in cyclocondensation reactions. The use of ionic liquids as solvent with a molar ratio of 1:10 (reactant:IL) was investigated in the synthesis of imidazo[1,2-*a*]pyrimidines **16** and imidazo[1,2-*a*]pyridines **15**, respectively, from the cyclocondensation of 2-aminopyrimidines **11** or 2-aminopyridines **10** with a suitable α-bromoacetophenone **12-14** [Enguehard et al., 2003]. The authors found that α-tosyloxylation (bromination) of ketones can be performed by treating the ketones with HTIB ([hydroxyl(tosyloxy)iodo]benzene) and 2-aminopyrimidine successively in [BPy][BF_4]. Consequently, the authors reasoned that imidazo[1,2-*a*]pyrimidine **15,16** could be directly prepared by a one-pot procedure. In all of these cases, the ionic liquid was reused four times with a gradual loss of activity (90, 86, 85, 80% yields). The reaction performed in ILs showed rate acceleration and increased yield, when compared with the reaction performed with molecular solvents, such as acetonitrile, where the preparation of imidazo[1,2-*a*]pyridines **15** required refluxing for 6-24 hours and the yield was only 37% [Bienaymé & Bouzid, 1998]. For the preparation of 2-phenylimidazo[1,2-*a*]pyrimidines **16**, refluxing for 6 h in a molecular solvent such as ethanol was necessary [Enguehard et al., 2003].

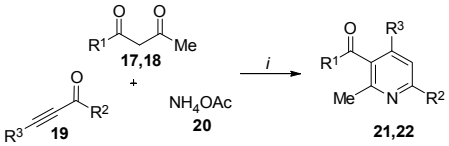
We consider important to show that task-specific ionic liquids also have applications in heterocyclic synthesis. [HMIM][Tfa] was designed as a protic ionic liquid [Greaves & Drummond, 2008] and Karthikeyan and Perumal [Karthikeyan & Perumal, 2005] proposed



R^1 = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-Me-Ph, 4-MeO-Ph, Fur-2-yl, Benzo[*b*]fur-2-yl; R^2 = H, Me; R^3 = H
10,15 (X = CH) **11,16** (X = N) **12** (Y = OTs) **13** (Y =Br) **14** (Y =H)
i: Na_2CO_3, [BPy][BF_4], r.t., 1 h (**15** 56-90%).
ii: HTIB, Na_2CO_3, [BPy][BF_4], r.t., 1 h (**16** 72-85%).

Scheme 2

a methodology using this ionic liquid for the synthesis of pyridines **21,22**, by generating the enaminone from the corresponding β-ketoesters **17,18** for an *in situ* heteroannulation in the Bohlmann-Rahtz reaction. The one-pot, three component reaction of 1,3-dicarbonyl compounds **17,18**, ammonium acetate **20**, and alkynones **19** in [HMIM][Tfa] as solvent gave good results (Scheme 3). Although the reaction time using the ionic liquid was longer than other methods described in the literature, this synthetic route was considered simpler and more convenient. In molecular solvents such as EtOH (temperature 140-160°C) and toluene (it was necessary to add AcOH (5:1) or a Lewis acid such as $ZnBr_2$), the reaction time was 5.5 h (in both cases) [Bagley et al., 2006].

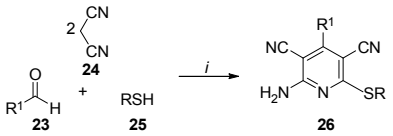


17,21 (R^1 = OMe, OEt) **18,22** (R^1 = Me)
R^2 = Me, Ph; R^3 = H, Ph, $SiMe_3$
i: [HMIM][Tfa], r.t., 24 h (80-94%).

Scheme 3

On the other hand, although some authors do not classify [BMIM][OH] as a basic ionic liquid [MacFarlane et al., 2006], it was used as a base IL in a protocol to synthesize polyfunctionalized pyridines by a cyclocondensation reaction [Ranu et al., 2007]. The conventional method for this reaction involves the condensation of aldehydes **23**, malononitrile **24**, and thiols **25** to afford highly substituted pyridines **26** (Scheme 4). One of the serious limitations of the conventional procedure is the formation of considerable amounts of a side product, enaminonitrile, reducing the yields of the pyridines to 20-48% when using bases such as DABCO (1,4-Diazabicyclo[2.2.2]octane) and Et_3N in ethanol under reflux (2-3 h) [Evdokimov et al., 2006]. Ranu et al. [Ranu et al., 2007] demonstrated that the ionic liquid [BMIM][OH] completely suppressed the side reaction that formed enaminonitrile and raised the (isolated) yields of pyridines to a level of 62-95% (Scheme 4). A wide range of substituted aromatic and heteroaromatic aldehydes **23** as well as several substituted thiophenols **25** underwent this three-component condensation with malononitrile. The ionic liquid was used at a molar ratio of 1:0.5 (reactant:IL) and the authors claimed that the presence of the ionic liquid, [BMIM][OH], was essential, as the reactions did not proceed at all in its absence. The use of other ionic liquids such as

[BMIM][Br] or [BMIM][BF_4] failed to push the reaction to the pyridine stage, and the reaction was stopped at an intermediate step with the formation of arylidenemalononitrile.



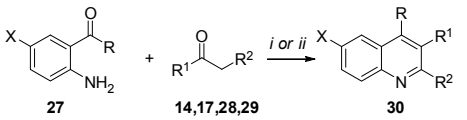
R = Ph, 4-Cl-Ph, Tol-4-yl, Tol-2-yl;
R^1 = Ph, 4-Me-Ph, 4-MeO-Ph, 3-MeO-4-HO-Ph, 2-Br-Ph, 3-Br-Ph, 4-Cl-Ph, 2,6-Cl_2-Ph, 4-O_2N-Ph, 4-MeS-Ph, 4-HO-Ph, Benzodioxol-1,3-yl, Thien-2-yl
i: [BMIM][OH]/EtOH, r.t., 1-2 h (65-95%).

Scheme 4

Protic ionic liquid [HBIM][BF_4] has been reported in the synthesis of quinolines [Palimkar et al., 2003]. The Friedländer heteroannulation protocol was used in ionic liquids at a molar ratio of 1:1 (reactant:IL), which made another catalyst unnecessary for the preparation of **30** (Scheme 5). Two sets of ionic liquids based on BBIM and HBIM salts were used. The capacity of the ionic liquids to promote these heterocyclization reactions was correlated to the basicity of their anions. The authors assumed that the nature of the anion governed the electrophilicity of the imidazolium cation, which in turn had a bearing on the acidity of the ionic liquid. It was observed that the higher the basicity of the anion (increasing pKa of the corresponding acid) the greater the increase in yield. [HBIM][BF_4] afforded the best result and, consequently, all further studies were conducted using this ionic liquid as the reaction medium. The ionic liquid was recovered and reused twice with no appreciable decrease in yield.

Karthikeyan [Karthikeyan & Perumal, 2004] investigated the quinolines synthesis using a [BMIM][Cl]:$ZnCl_2$ melt (1:2 molar ratio), which can act as both a solvent and catalyst on account of its high polarity and Lewis acidity. 2-Aminoketones **27** and ketones/ketoesters **14,17,28,29** were mixed in the [BMIM][Cl]:$ZnCl_2$ melt and stirred at room temperature for 24 h to give quinolines **30** in good to excellent yields (Scheme 5). The ionic liquid was recovered and reused twice with no appreciable decrease in the yield of **30** (89%, 86%). Theoretically, the Friedländer reaction with unsymmetrical ketones such as ethyl methyl ketone can have two possible modes of cyclization giving rise to two regioisomers, 2,3-dimethylquinoline and 2-ethylquinoline, respectively. The reaction path suggested for the Friedländer synthesis involved a sequential formation of the *N*-(2-acylphenyl)-β-enaminone/cyclodehydration reaction. The ionic liquid, promoting the Friedländer reaction with unsymmetrical ketones, regiospecifically afforded the 2,3-dialkylquinolines **30** in excellent yields. The author mentioned that polarity and the large electrochemical window of the ionic liquid may have also contributed to the observed regiospecificity. In the case of 2-aminoacetophenones **27**, the corresponding quinolines **30** were synthesized in excellent yields, that were in fact superior to those reported from conventional procedures using molecular solvent as ethanol under reflux for 12 h [Das et al., 2007].

From these examples, it can be found that for cyclocondensation reactions, ILs have designated present functions of solvent-catalyst, liquid support and co-promoters of the reaction by their task-specific acid or base functions (**Figure 2**). However, in answering the above-mentioned question of whether ILs are catalysts or solvents, based on this important finding and numerous other results collected in our review, we believe that the best approach to it is considering the ionic liquid as a solvent.



14,30 (R^2 =H) **17,30** (R^2 = CO_2Et) **27,30** (R = Me, Ph; X = H, Cl)
28,30 (R^1 = Me, Ph, 4-Cl-Ph, 4-Br-Ph; R^2 =H, Me, $COCF_3$, $PhCH_2$)
29,30 R^1, R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-,
i: [HBIM][BF_4], 100°C, 3-6 h (90-97%).
ii: [BMIM][Cl]:$ZnCl_2$, r.t., 24 h (55-92%).

Scheme 5

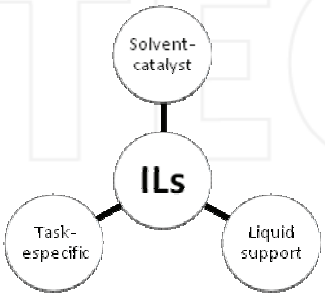
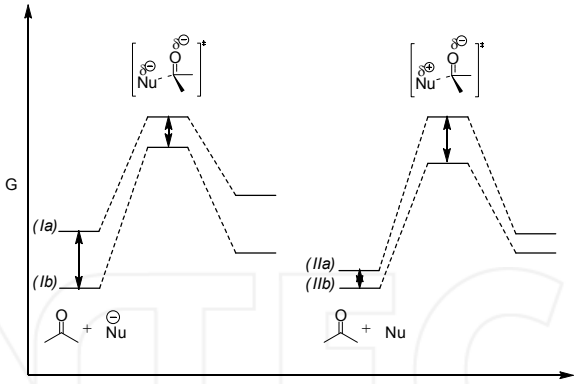


Fig. 2. IL effects in cyclocondensation reactions.

Considering the ionic liquid as a solvent, a single parameter of "polarity", "solvent strength", or "interaction" is not sufficient to explain the variation in experimental results in the many solvent-mediated processes. However, it is reasonable to postulate that the enhanced rate of the reactions is a result of the decrease of activation energy of the slow reaction step, which in turn is most likely due to the general ionic liquid effect. This can be expected for reactions involving highly polar or charged intermediates, such as carbocations or carbanions, and activated complexes, which could become more stable and long-lived in this media [Olivier-Bourbigou & Magna, 2002]. The influence of solvents on rate constants can be understood in terms of transition-state theory. According to this theory, solvents can modify the Gibbs energy of activation (as well as the corresponding activation enthalpies, activation entropies, and activation volumes) by differential solvation of the reactants and the activated complex. The effect of the solvent on reactions was investigated by Hughes and Ingold. They used a simple qualitative solvation model considering only pure electrostatic interactions between ions or dipolar molecules and solvent molecules in initial and transition states [Hughes & Ingold, 1935] and postulated that a change to a more polar solvent will increase or decrease the reaction rate depending on whether the activated reaction complex is more or less dipolar than the initial reactants (**Figure 3**). In this respect, the term "solvent polarity" was used synonymously with the power to solvate solute charges. It was assumed to increase with the dipole moment of the solvent molecules and to decrease with increased thickness of shielding of the dipole charges.

In summary, Welton and Oliver-Borbigou gave a superficial explanation of the role of ILs in organic reactions, asserting that they have a dual action of solvent-catalyst. Lee *et al.* also attempted to explain this, though they limited their explanation to stating that the effects of ILs on organic reactions were due to the stabilization of the reaction transition state. We



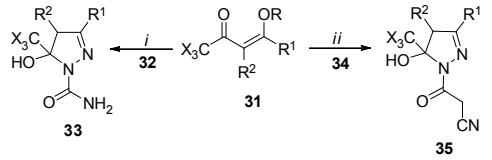
(a) Non polar solvents, and (b) polar solvents.

Fig. 3. Schematic Gibbs energy diagram for a general nucleophilic addition to carbonyl carbon.

have offered a more complete explanation by maintaining that the positive effects of ILs on cyclocondensation reactions are due to the fact that they cause a decrease in the activation energy of the slow reaction and a stabilization of transition states and highly polar or charged intermediates, such as carbocations and carbanions.

In our work, we have also performed an investigation in the Web of Science to show a proliferation of papers in the area of ionic liquids. We found more than 12,000 papers published in the period from 1990 to August 2010, in which more than 95% of the papers were published after the year 2000. These data show the increase in new researchers entering the area. On the other hand, less than 1% of all the papers published in the mentioned period dealt with the application of ionic liquids in heterocyclic synthesis from cyclocondensation reactions! This fact demonstrates that there is a lack in the literature of reports dealing with this theme, in particular on the synthesis of pyrazoles in ionic liquid media. Taking into account the importance of heterocycles, in special pyrazoles, and the environmental and economic need of their obtainment in a highly regioselective manner, and in accordance with works that we have developed in our research for more than twenty years, we decided to contribute to the research on ionic liquid effects in pyrazole synthesis by cyclocondensation reactions.

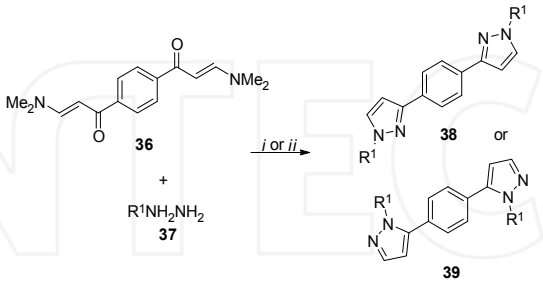
Our first work to this aim was published together with our review [Martins et al., 2008] and reported the synthesis of 4,5-dihydropyrazoles **33** from the reaction of enones **31** with hydrazine **32** in the presence of the ionic liquid [BMIM][BF_4]. The reaction was performed at 80°C during 1 h. The yields were higher and the reaction time was shorter in comparison to those found for the conventional method (MeOH, reflux, 16 h, 65-73%). (Scheme 6, *i*) [Sanin et al., 1998]. Later, we [Moreira et al., 2008] also employed ILs in the synthesis of 4,5-dihydropyrazoles **35** from the cyclocondensation reaction of enones **31** and cyanoacetohydrazide **34**. The reaction was carried out in [BMIM][BF_4], containing a catalytic amount of HCl conc., at 50°C, during 10-180 min, and the products were obtained in reasonable to good yields. The ionic liquid was used at a molar ratio of 1:1 (reactant:IL). It was possible to affirm that the IL [BMIM][BF_4] allowed the reaction to proceed in a shorter time than when the reaction was carried out in molecular solvents, even when a Brønsted catalyst (HCl) was present.



R = Me, Et R^1 = H, Me, Ph R^2 = H, Me
i: $NH_2NHCONH_2$, [BMIM][BF_4], 80°C, 1 h (73-86%)
ii: $NH_2NHCOCH_2CN$, [BMIM][BF_4], HCl, 50°C, 10-180 min (62-95%)

Scheme 6

In our continuing interest to demonstrate the effects of ILs on pyrazole synthesis, we used ionic liquid to promote cyclocondensation reactions to form bis-pyrazoles **38,39** from the reaction of enaminoketones **36** and a series of aryl and alkyl hydrazines **37** [Moreira et al., 2010]. In each case, three ionic liquids ([BMIM][BF_4], [HMIM][HSO_4] and [BMIM][OH]) were evaluated, and the first two proved to be the most suitable for these cyclocondensation reactions. The ionic liquid was used at the same molar ratio of the reactants **36** and **37** and the reactions were performed at 70-90°C (Scheme 7). We found that the catalytic power of [BMIM][BF_4] was improved when the acid HCl was employed. On the other hand, the use of [HMIM][HSO_4], an ionic liquid that combines polar properties with the Brønsted acidic function, promoted these reactions without the need of a co-catalyst. These reactions were performed in molecular solvents such as EtOH, DMF and H_2O, however, the results were unsatisfactory, leading to a lower regioselectivity and a longer reaction time.
In this same context, we published a study where a series of ten imidazolium-based ionic liquids ([BMIM][BF_4], [BMIM][Br], [OMIM][BF_4], [BMIM][PF_6], [DBMIM][Br], [DBMIM][BF_4], [BMIM][OH], [BMIM][SCN], [HMIM][HSO_4] [HMIM][CF_3CO_2]) was evaluted in the promotion of the cyclocondensation reaction of enaminones **40** and *t*-butyl hydrazine **41** (Scheme 8) to form pyrazole **42** [Frizzo et al. 2009]. The best result was achieved when the ionic liquid [BMIM][BF_4] was employed as the reaction media. Either the aryl-, heteroaryl-, alkyl-, or heteroalkyl β-dimethylaminovinyl ketone reacted with *t*-butylhydrazine hydrochloride **41** smoothly at 80°C for 1 h.



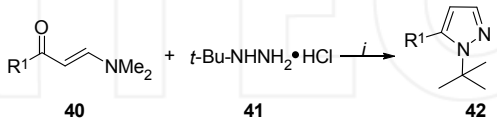
R^1 = H, Ph, 4-O_2N-Ph, 2,4-(O_2N)-Ph, C_6F_5, CO_2Me, $CONH_2$, CH_2CH_2OH, *t*-Bu
i: HCl or BF_3•OEt_2, [BMIM][BF_4], 70-90°C, 0.5-2 h (70-84%)
ii: [HMIM][HSO_4], 90°C, 0.5-3 h (60-88%)

Scheme 7

The reaction of 1-aryl- and 1-heteroaryl-substituted-β-dimethylaminovinyl ketones furnished the products **42** in good to excellent yields. On the other hand, the reaction of 1-hexyl-β-

dimethylaminovinyl ketone with *t*-butylhydrazine proceeded, but the product was obtained as a mixture of 1,3- and 1,5-isomers at a ratio of 7:1, respectively. Therefore, it seems that the presence of an alkyl substituent makes the carbonyl carbon of β-dimethyl aminovinyl ketone as reactive as the carbon with carbonyl aryl- and heteroaryl substituents, leading to a mixture of isomers. The ionic liquid was used at the same molar ratio of the reactants. The recyclability and the reuse of the ionic liquid [BMIM][BF_4] was also investigated and it was found that the ionic liquid could be used for several runs without loss of activity. Reaction of **40** and **41** was also performed in ethanol, using the same reaction conditions, however, it led to the products in lower yields than those found with [BMIM][BF_4].

We went on to study the effect of ILs in cyclocondensation reactions to synthesize pyrazole by the evolution of [BMIM][BF_4] in the reaction of enones **31** and *t*-butyl hydrazine **41** to synthesize a series of 3(5)-trifluoromethylpyrazoles **43**, **44** (Scheme 9).

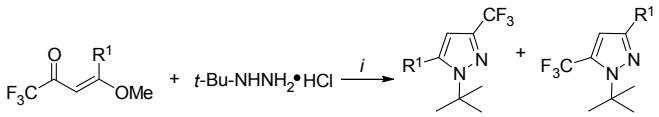


40 **41** **42**

R^1 = Ph, 4-Br-Ph, 4-Cl-Ph, 4-F-Ph, 4-O_2N-Ph, 4-Me-Ph, Fur-2-yl, Thien-2-yl, Pyrrol-2-yl, Pyrid-2-yl, Hexyl.
i: [BMIM][BF_4], 80°C, 1 h (72-96%)

Scheme 8

The reaction was carried out at 78°C during 15 h, using the ionic liquid at a molar ratio of 1:2 in relation to the reactants. The products were obtained as a mixture in good to high yields (70-93%). The *1,5*-isomer was preferentially formed in ILs for most groups in R^1, as shown in Scheme 9. The presence of pyridine was necessary considering the loss of the t-butyl group when this base was not employed.



31 **41** **43** **44**

i: Pyridine, [BMIM][BF_4], 78°C, 15 h.

R^1	Molar Ratio **43**:**44**	Yield (%)[a]
Ph	15:85	85
4-Me-Ph	43:57	72
4-MeO-Ph	44:56	72
4-F-Ph	30:70	81
4-Cl-Ph	36:64	93
4-Br-Ph	39:61	93
Fur-2-yl	25:75	70
Thien-2-yl	57:43	75
Naphth-2-yl	47:57	84

[a] Yields of isolated product

Scheme 9

3. Cycloaddition reactions

A cycloaddition reaction is a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine, with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. Cycloadditions provide unsaturated or partially saturated (hetero) cycles with well-defined substitution patterns and often with high stereocontrol. For example, the Diels-Alder reaction has many examples that form heterocyclic as well as carbocyclic ring systems. This half of the literature is about [3+2] cycloaddition reactions which form 5 membered ring heterocyclic systems, in an analogous way to the [4+2] Diels-Alder process which forms 6-membered rings. The reactive partners in this reactions are 1,3-dipoles and dipolarophiles in 1,3-dipolar cycloadditions and diene and dienophile in the Diels-Alder reaction. There are also [2+1] cycloadditions that furnish aziridines and [2+2] cycloadditions that provide β-lactams. The Diels–Alder reaction (DA) [4+2] cycloaddition is one of the most intensively studied organic reactions, not only from a synthetic standpoint [Fringuelli & Taticchi, 2002] [Ibrahim-Ouali, 2009], but also from a theoretical point of view [Apeloig & Matzner, 1995][Imade et al, 1999]. From studies of cycloaddition reactions, in particular Diels-Alder reactions, have established that reactions between dienes (dipoles) and dienophiles (dipolarophiles) fit into the following general profile: (a) it is currently accepted that cycloadditions are concerted processes; they have no distinct intermediates, but the bond formation may be asynchronous; (b) the reaction rates are not influenced much by solvent polarity indicating little change in polarity between reactants and transition state; (c) rates of reaction between dienes (dipoles) and dienophiles (dipolarophiles) vary considerably. This can be explained by the Frontier Molecular Orbital Theory, which considers the interaction between molecular orbitals of the dienes (dipoles) and dienophiles (dipolarophiles).

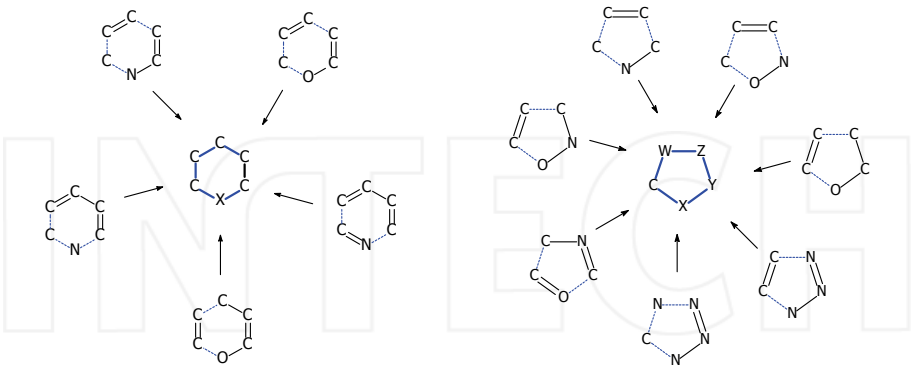
3.1 Characterization of cycloaddition reactions

Among the cycloaddition reactions, 1,3-dipolar reactions have had an extensively successful history of use in heterocyclic synthesis. The 1,3-dipole is typically represented by closed-shell all-octet valence structures (I). They could be atmospheric components such as ozone (O_3) and nitrous oxide (N_2O), or highly popular azides (N_3R). The [4+2] thermal cycloadditions of 1,3-dipoles with alkene and alkyne dipolarophiles generate six- and five-membered heterocycles and are called 1,3-dipolar cycloadditions because of the dipolar nature of the principal resonance structures and the 1,3-additions that they undergo (**Figure 4**) [Huisgen, 1999].

I

The series depicted in **Figure 4** was constructed from the literature found for 1,3-dipolar cycloaddition reactions in ILs. Reactions were performed with different 1,3-dipoles and dipolarophiles. In general, dipolarophiles, as the C=C block, were enol ethers, alkenes, alkynes, α,β-unsaturated carbonyl or nitrile compounds, and nitriles and imines were the C≡N and C=N blocks, respectively. The blocks that most frequently represented 1,3-dipoles were enamines (C=C-N), ketones (C-C=O), aminoketones (N-C), hydroxylamines (N-O), aldoximes (O-N=C) and azides (N=N-N). In some cases, the 1,3-dipolar cycloaddition had

multiple components, with blocks of one atom such as chloroamine-T (N), amine (N), aldehyde (C), enol ether (C) and orthoformate (C). Dipoles vary greatly in stability. Some can be isolated and stored, others are relatively stable, but are usually made on the same day of their use. Others are so unstable they are generated and reacted *in situ*.



(a) X = O, N (**b**) X = O, N Y, Z, W = C, N

Fig. 4. General 1,3-dipolar cycloaddition and possible combination to form (a) six-membered and (b) five-membered heterocycles.

Table 3 shows the reaction type and building blocks that are found in 1,3-dipolar cycloadditon reactions for heterocyclic synthesis in ILs. The first three columns illustrate the chemical functions of the building blocks of dipolarophiles and 1,3-dipoles and the respective atoms involved in heterocyclic formation. The last column demonstrates the products. We designed Table 3 considering the expanded generalization and classification of 1,3-dipolar cycloadditions. From this classification, for so-called 1,3-dipoles "with a double bond"(I), atoms X and Z can be C, N, or O, while the center atom Y is nitrogen. These are typically referred to as propargylic species and have two sets of degenerate π-orbitals in a linear structure. Dipoles "without a double bond" may have a nitrogen function or oxygen atom at the central position and are isoelectronic with the allyl anion.

3.2 Ionic liquids in cycloaddition reactions

Since Breslow and Rideout [Rideout & Breslow, 1980] evidenced the dramatic accelerating effect of water on cycloaddition reactions in 1980, the solvent effect in this reaction received more attention. Diels–Alder reactions, for example, proceed at an appreciable rate only when either the diene or the dienophile are activated by an electron-donating or electron-withdrawing group, normally characterized by the presence of a heteroatom that can therefore efficiently interact with the solvent. Desimoni et al. [Desimoni et al., 1990] studied the solvent-substrate interaction in Diels–Alder reactions and classified these reactions into three types. Type A is characterized by an increase of the rate constant upon increasing the acceptor number (AN) power of the solvent. This behavior has been attributed to $LUMO_{solvent}$–$HOMO_{solute}$ interactions and considered similar to Lewis acid catalysis. Type B is dominated by the electron donation ability of the solvent, which decreases the reaction rate by soft–soft interactions: $HOMO_{solvent}$–$LUMO_{solute}$ interactions have been considered responsible for this effect. Type C includes all reactions that show a small solvent effect (for example, cyclopentadiene dimerization). In this case, solvent–solvent interactions are dominant.

Blocks	Blocks	Blocks	Product
Enol ether (C=C)	Enamine (C=C-N)	Aldehyde (C)	Tetrahydroquinolines
Enol ether (C=C)	Enamine (C=C-N)	Enol ether (C)	Tetrahydroquinolines
Enol ether (C=C)	Enamine (C=C-N)	Aldehyde (C)	Tetrahydroquinolines
Alkene (C=C)	Enamine (C=C-N)	Aldehyde (C)	Octahydroacridines
Alkene (C=C)	Enamine (C=C-N)	Aldehyde (C)	Tetrahydroquinolines
Alkene (C=C)	Ketone (C-C=O)	Aldehyde (C)	Coumarins
Fullerene (C=C)	Aminoketone (N-C)	Aldehyde (C)	Pyrrolidine
α,β-Unsaturated carbonyl compounds (C=C)	Hydroxylamine (N-O)	Aldehyde (C)	Isoxazolidine
α,β-Unsaturated nitrile compounds (C=C)	Hydroxylamine N-O	Aldehyde (C)	Isoxazolidine
Alkoxydiene (C=C-C=C)	Amine (N)	Aldehyde (C)	Pyridone
Azide (N=N-N)	Amine (N)	Orthoformate (C)	Tetrazole
α,β-Unsaturated carbonyl compounds (C=C)	Aldoxime (O-N=C)	-	2-Isoxazoline
α,β-Unsaturated nitrile compounds (C=C)	Aldoxime (O-N=C)	-	2-Isoxazoline
Heterosubstituted Alkene (C=C)	Aldoxime (O-N=C)	-	2-Isoxazoline
Enol ether (C=C)	Nitrone (O-N=C)		Isoxazolidine
Alkene (C=C)	Chloroamine-T (N)	-	Aziridine
α,β-Unsaturated carbonyl compounds (C=C)	Chloroamine-T (N)	-	Aziridine
Alkene (C=C)	1,4-benzoquinone (C-CO)	-	2,3-Dihydrobenzofuran
Alkene (C=C)	2-Hydroxyaldehyde (C=C-O)	-	Benzopyran
Nitroenamine (C=C)	Arylazide (N=N-N)	-	1,2,3-Triazole
Alkyne (C≡C)	Arylazide (N=N-N)	-	1,2,3-Triazole
Alkyne (C≡C)	Alkylazide (N=N-N)	-	1,2,3-Triazole
Alkyne (C≡C)	Azide (N=N-N)	-	1,2,3-Triazole
Nitrile (C≡N)	Azide (N=N-N)	-	Tetrazole
Nitrile (C≡N)	Azide (N=N-N)	-	Tetrazole
Imine (C=N)	Acid chloride (C-C)	-	Lactam
Imine (C=N)	Diene (C=C-C=C)	-	Tetrahydroquinolines
Imine (C=N)	Alkoxydiene (C=C-C=C)	-	Pyridone
Aldehyde (C=O)	Imidate (C=N-C)	-	Oxazoline

Table 3. Building blocks and products of 1,3-dipolar cycloaddition reactions in ILs.

Actually, the cohesive energy density (ced) (not to be confused with the internal pressure) together with the solvent H-bond acidity (α), has been shown [Gajewski, 1992] to also affect Diels–Alder Type A reactions, whereas in the special case of intramolecular Diels–Alder reactions in highly viscous media, Firestone *et al.* have demonstrated [Firestone & Saffar, 1983] the importance of solvent density. The considerations about the influence of ced on the reaction rate of cycloadditions raise the issue of solvophobic interactions, which are essentially being quantified by the ced. These parameters are also considered to determine the water effect. In terms of TS theory, hydrophobic hydration raises the initial state more than the TS and hydrogen bonding interactions stabilize the TS more than the initial state.

Highly polarizable activated complexes play a key role in these effects [Otto & Engberts, 2000].

Recently, Chiappe *et al*. [Chiappe et al., 2010] published a review about solvent effect on the Diels-Alder reactions in ILs. In this work, the authors discussed the role of ILs in these reactions considering multiparameter linear solvation energy relationships and theoretical analysis. The authors proposed that the endo:exo ratio and associated acceleration observed in the Diels–Alder addition of cyclopentadiene with methyl acrylate was attributed to the ability of the IL to hydrogen bond to the dienophile (methyl acrylate), a process considered to be determined by two competing equilibria. The IL cation ($[BMIM]^+$) can form a hydrogen bond to the anion of the IL (Eqn 1) or to the methyl acrylate (MA) (Eqn 2).

$$[BMIM]^{\oplus} + A^{\ominus} \rightleftharpoons [BMIM]^{\oplus}\cdots A^{\ominus} \quad (1)$$

$$[BMIM]^{\oplus} + MA^{\ominus} \rightleftharpoons [BMIM]^{\oplus}\cdots MA \quad (2)$$

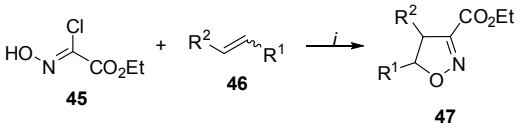
Therefore, the authors proposed that the concentration of the hydrogen-bonded cation–methyl acrylate adduct is inversely proportional to the equilibrium constant for the formation of the cation–anion hydrogen-bonded adduct (K_1). In light of the more recent data on IL structure [Chiappe, 2007] they suppose that the interaction of the cation with reactants and/or the TS implies a reduction of the interactions of this cation with the surrounding anions. The dissolution of a substrate in a solvent, also including ILs, can be represented as follows: a "cavity" is created in the solvent to insert the substrate, and subsequently the reorganization and reorientation of the solvent around the solute occurs [Bruzzone & Chiappe, 2008]. In agreement with the system represented by Eqn 1 and Eqn 2, a strong interaction between IL cations and anions hinders the formation of the cavity, and reduces the rate of reorganization and reorientation of cations and anions around the reactants, thus decreasing the possibility for the cation (or anion) to solvate the reactant and/or the TS. However, the situation is much more complicated than that represented by Eqn 1 and Eqn 2, involving a system more complex than an ion pair, and in which kinetic effects also play a role during the solvent reorganization and reorientation. Also, in this review, Chiappe *et al*. [Chiappe et al., 2010] reported the more important findings of theoretical studies on Diels-Alder reactions in ILs. The main results of this investigation revealed that the Diels–Alder reaction in the presence of the imidazolium cation proceeds via a concerted mechanism similar to the "uncatalyzed" cycloaddition, although the asynchronicity of the process is increased by the presence of the imidazolium cations. The energetic differences between the reactants and the TSs for the endo and exo approaches, calculated for the three dienophiles in the presence of the above-mentioned cations, were qualitatively in agreement with the experimental data and confirmed the high selectivity in favor of the endo path for the reaction of cyclopentadiene with acrolein or methyl acrylate in a [HBIM]-based IL [Chiappe et al., 2010]. On the basis of these data, it was hypothesized that the interaction between the IL cation and the dienophile may be affected by the whole ionic system, and the expression "clamp-effect" was used to define this interaction. More specifically, the IL cation interacts with the dienophile acting as a "clamp", since in an IL, the freedom of motion of the cation is strongly limited by Coulombic interactions with the solvent bulk, which can be considered the clamp support. Therefore, the consequences of cation–dienophile interaction and of the clamp effect on Diels–Alder reactions is, from a simplistic view, that the

interaction with the cation determines the polarization of the double bond of the dienophile, increasing its reactivity, whereas the clamp effect blocks one of the reactants, increasing the probability of efficient stacking in the TS. Another finding verified by Chiappe *et al.* [Chiappe et al., 2010] was that the presence of the IL changes the geometry of the TS for all four pathways considered, deforming the diene–dienophile stacking geometry and enhancing the asynchronicity of the reaction when performed in these solvents. Before examining in detail the solvation aspects, it is necessary to recall that the insertion of a solute in a solvent is characterized by a free energy of solvation that can be approximately divided in two parts: the change in electronic energy of the solute given by electrostatic and dispersion interactions with the solvent, and the change of solvent energy due to the necessary reorganization of the solvent molecules in order to embed the solute. The most important solvent effect on the reaction rate emerging from these calculations is given by the solvation free energy, which promotes the aggregation of non-ionic compounds. This "solvophobic" effect, which can be considered similar to that of water, arises from the fact that the (generally positive) solvation free energy of a neutral solute in an IL is dominated by the unfavorable process of creating a cavity of suitable size to accommodate the solute. This process in ILs requires a considerable amount of work due to the lowering of the Coulombic interactions, which cannot be recovered by dipole–ion (or even less efficient) interactions. This discussion is detailed in the work of Chiappe *et al.* [Chiappe et al., 2010].

As we have performed a survey about ionic liquids in heterocyclic synthesis by cyclocondensation reaction, likewise we have addressed cycloaddition reactions. The most important contributions were reported the role of ionic liquids in these reactions, in accordance with Chiappe *et al.* [Chiappe et al., 2010] was discussed.

Here, we have compiled the most important results, and we will briefly describe the reactions where ILs have had remarkable effects, such as rate increase, higher yields and endo/exo selectivity. An important effect of IL in the synthesis of isoxazoline dicarboxylates from the cycloaddition of carboethoxyformonitrile oxide (CEFNO) with different dipolarophiles (e.g., diethyl malonate and acrylonitrile) (Scheme 10), reported by Conti *et al.* [Conti et al., 2003] was the decrease of the by-product furoxane. The reaction conditions involved equimolar amounts of **45**, **46** and $KHCO_3$ in ionic liquid (molar ratio of 1:1.4/reactant:IL). The products were obtained in good yields with electron-rich alkenes and even conjugated dipolarophiles, however the authors also observed the formation of the sub-product furoxane in small amounts, which was formed by dimerization of unstable CEFNO that did not conclude the cycloaddition with acrylate. Probably, the presence of the ionic liquid in basic medium induced the thermodynamically unfavorable migration of the double bond to the terminal position, generating a more reactive alkene that immediately gave rise to cycloaddition. The authors also reported attempts to obtain compounds **47** with diethyl ether as solvent, however this route produced the required products in low yields (20–30%) together with larger amounts of furoxane, even when large amounts of the dipolarophile (45%) were used [Conti et al., 2003].

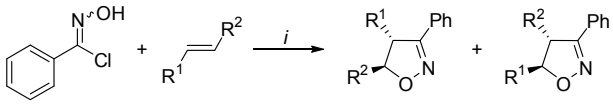
The better selectivity of cycloaddition reactions was reported by Rosella and Harper [Rosella & Harper, 2009] who performed cycloaddition reactions between benzonitrile oxide, generated *in situ* from the corresponding chloroaldoxime **48** and substituted alkenes (Scheme 11). Initially, the authors performed the cycloaddition reaction with alkene **46** (where, R^1 = Ph; R^2 = CO_2Et), that bear electronic and steric effects, and benzonitrile oxide **48** in three ionic liquids. The authors observed that the reaction in [BMIM][PF_6] furnished a mixture of 4,5-dihydroisoxazoles in a molar ratio of 1:>12 (9:10) and the best conversion



R^1 = CO_2Et, CO_2Bn, CN, CH_2CN, $OC(O)CH_3$, $SiMe_3$, CH_2Cl;
R^2 = H, *cis*-CO_2Et, *trans*-CO_2Et, *trans*-Me; R^1,R^2 = 2,3-Dihydrofuran, *c*-hexene.
i: $KHCO_3$, [BMIM][BF_4] or [BMIM][PF_6], r.t., 5-12 h (55-95%).

Scheme 10

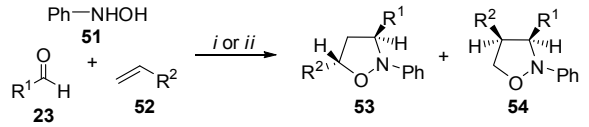
(84%), when compared with the two other ionic liquids. The conversion in the water-soluble ionic liquid [BMIM][$N(CN)_2$] was very small and thus was disregarded. Steric interactions in the transition state leading to the isomers **49** and **50** are more significant in ionic liquids than they are in molecular solvents. The authors argued that ionic liquid have higher cohesive pressures than molecular solvents [Swiderski et al., 2004]. The amount of reactant and ionic liquid employed was not informed. The authors also performed this reaction in three molecular solvents (acetonitrile, ethyl acetate and THF) and observed similar diastereoisomeric ratios for products 4**9** and **50** (when R^1 = Me, Et and R^2 = CO_2Et, CH_2OH), however they presented lower molar ratios in regard to the product with R^1 = Ph and R^2 = CO_2Et. The difference between the reaction outcomes in the two ionic liquids is small when compared to the differences between ionic liquids and molecular solvents.



R^1 = Me, Et, Ph; R^2 = CO_2Et, CH_2OH
i: Et_3N, IL, r.t., 12-24 h

Scheme 11

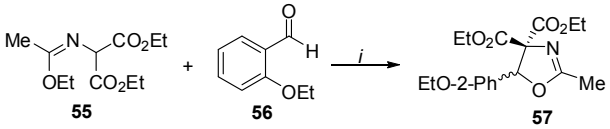
Ionic liquids were found to reduce reaction time and to give better regioselectivity than organic solvents, as presented by Yadav *et al.* [Yadav et al., 2007] in the synthesis of isoxazolidines from 1,3-dipolar cycloaddition reactions of nitrones with electron deficient olefins (Scheme 12). The reaction between aldehyde, *N*-phenylhydroxyl amine and acrylonitrile was carried out in both hydrophilic and hydrophobic ionic liquids, ([BMIM][PF_6] or [BMIM][BF_4]), at room temperature during 4-6 h. The reactants **51**, **52** and **23** and the ionic liquid were used at a molar ratio of 1:1:1.2:10, respectively. Similar results in regard to the reaction rates and yields were obtained in both ionic liquids. The authors believe that the anticipated 1,3-dipoles exhibit enhanced reactivity in ionic liquid thereby reducing the reaction times and improving the yields significantly. Furthermore, the ionic liquids were found to give better regioselectivity than organic solvents since the reaction of C,N-diphenyl nitrone with ethyl acrylate in [BMIM][BF_4] gave the products **53** and **54** in 90% yield at a ratio of 9:1 over 4 h, whereas the same reaction in refluxing benzene gave the desired products **53** and **54** in 68% at a 2:1 ratio after 10 h [Yadav et al., 2007].
In another interesting study that showed the acceleration of cycloaddition reactions in ILs, Dubreuil et al. [Dubreuil & Bazureau, 2000] developed a route to obtain 2-oxazolines **57**, through cycloaddition reaction between imidate **55** and substituted benzaldehyde **56**, which



R^1 = Styryl, Ph, 3-Cl-Ph, 3-O_2N-Ph, 4-Cl-Ph, 4-MeO-Ph, 3,4-$(Cl)_2$-Ph, Benzo[3,4]dioxan-2-yl, Fur-2-yl; R^2 = CN, CO_2Me, COMe
i: [BMIM][BF_4], r.t., 4-5 h (85-93%)
ii: [BMIM][PF_6], r.t., 4.5-6 h (80-92%)

Scheme 12

acts as a dipolarophile (Scheme 13). Initially, the authors investigated the reaction of equimolar amounts of imidate **55** with 2-ethoxybenzaldehyde **56**, in different ionic liquids, maintaining the same temperature (70°C) in all tests. It was observed that the best rate acceleration was in the ionic liquid [EMIM][BF_4], due to the lower time (3 h) required for this reaction when compared with [EMIM][PF_6], which required 10 h for total conversion of the starting material. The addition of 5% of glacial acetic acid as Brønsted catalyst in the ionic liquid increased the reaction rate. However, the product yield was better when the ionic liquid [EMIM][PF_6] was used. This method for the synthesis of oxazolines **57** using molecular solvents has not yet been described in the literature.

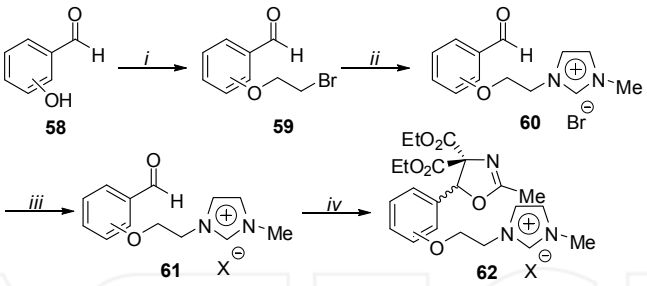


i: [EMIM][BF_4], 70°C, 3 h (70%)

Scheme 13

In a continuation, the authors explored the reactivity of benzaldehyde bound to the ionic liquid, furnishing the ionic liquid dipolarophiles **61** (X = BF_4, NfO), depicted in Scheme 14. The ionic liquid dipolarophiles **61** were reacted with imidate **55**, in equimolar amounts, under the same reaction conditions (70°C), although these reactions required different times. It is noteworthy that the reaction of imidate **55** with ionic liquid dipolarophile **61** was faster than the reaction of **55** with 2-ethoxybenzaldehyde **56** in [EMIM][NfO] ionic liquid. This acceleration observed with **61** is probably due to the intramolecular interaction between the CHO-group of the dipolarophile and the polar 3-methylimidazolium moiety.

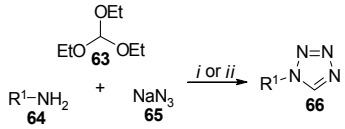
Potewar *et al.* [Potewar et al., 2007] claimed the efficacy of ionic liquids to promote cycloaddition reactions to be related to the correlation between the basicity of the anions of the ionic liquids as well as their polarity. They reported a one-pot condensation of sodium azide **65**, substituted amines **64** and triethyl orthoformate **63** in 1-butylimidazolium tetrafluoroborate ([HBIM][BF_4]) at 100°C to afford 1-substituted-1*H*-1,2,3,4-tetrazoles **66**, without any added catalyst (Scheme 15). A variety of amines, such as substituted anilines, heteroaromatic and aliphatic, was employed to investigate the scope of this process. The data obtained revealed that both anilines containing electron-withdrawing and electron-donating groups promoted the cycloaddition reaction in short reaction times (15-35 min) and in good yields (85-93%). The reactants amine, triethyl orthoformate, sodium azide and ionic liquid were used at a molar ratio of 1:1.2:1:3, respectively. The authors assumed that



X = BF_4, NfO
i: $Br(CH_2)_2Br$, NaOH, reflux, 48 h (61-67%)
ii: for **61** (position-2) 72 h; for **61** (position-4) 80°C, 15 h (94%)
iii: NH_4BF_4, H_2O, 60°C, 18 h (X = BF_4, Yield: 60-80%)
$C_4F_9SO_3K$, H_2O, 70°C, 18 h (X = NfO, Yield: 53%)
iv: imidate (**55**), 70°C, 6-7 h (conv. 64-80%).

Scheme 14

the nature of the anion would influence the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. They observed that with the increasing basicity of the anion (increasing pKa of the corresponding acid), there was a progressive increase in the yield. The [HBIM][BF_4] afforded the best results by virtue of its inherent Brønsted acidity. The conventional methods reported for the synthesis of tetrazoles use either acidic conditions involving acids, such as hydrochloric, acetic, trifluoroacetic, and sulfuric, or highly polar solvents, such as 2-methoxyethanol, DMF, or methanol, and require very harsh reaction conditions such as refluxing for 6–24 h [Potewar et al., 2007].

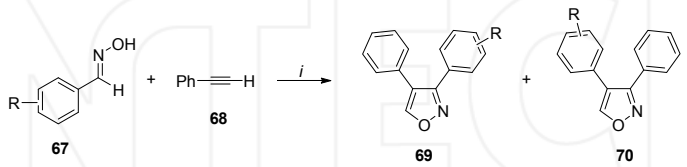


R^1 = Bn, Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, 3-Cl-Ph, 4-F-Ph, 3-Me-Ph, 3-Cl-4-F-Ph, 4-Ac-Ph, Pyrid-2-yl, 4-Me-Pyrid-2-yl, 6-Me-Pyrid-2-yl
i: [HBIM][BF_4], 100°C, 15-35 min (85-93%)
ii: [BBIM][Br]/DMSO, 30°C, 20-90 min (85-90%)

Scheme 15

Our contributions to studies of ionic liquid in heterocyclic synthesis by cycloaddition reactions are quite in beginning, we are preparing a review about heterocyclic synthesis by 1,3-dipolar cycloaddtion and we have performed a cycloaddition reaction between equimolar amounts of oximes **67** and phenyl acetylene **68** in presence of N-chlorosuccinimide and Et_3N in IL to produce isoxazoles **69** and **70** (Scheme 16). The IL was used in the same amount of the reactants. The reaction of oxime **68** (R = H), was also performed in reflux acetonitrile, for 5 h, however the product **69**, **70** was obtained in 70% of yield and in a molar ratio of 3:1 respectively.
In summary, from these examples, we found that the deployment of ILs in 1,3-dipolar cycloaddition reactions has brought about the reduction of reaction times, the increase of yields and better endo/exo selectivity in comparison to the use of molecular solvents. In

addition, from these important findings and numerous other results collected in the literature, we believe that the outstanding premises introduced by Chiappe *et al*. [Chiappe et al., 2010] for Diels-Alder reactions can be extended to the 1,3-dipolar cycloaddition reaction as a good approach to explain the solvent effect of ILs. Therefore, rate enhancements of 1,3-dipolar cycloaddition reactions in ILs could be ascribed to the same factors that are found in water: (*i*) increased polarity of the transition state, (*ii*) the hydrophobic effect which aggregates organic reactants raising the energy of the ground state relative to the transition state, thereby lowering the activation energy, and (*iii*) special or enhanced hydrogen bonding effects in the transition state.



i: NCS, Et_3N, [BMIM][BF_4], 90°C, 5h.

R	Molar Ratio 69:70	Yield (%)	R	Molar ratio 69:70	Yield (%)
H	10:1	84	4-Me	3:1	55
2-OH	5:1	42	2-Me	3:1	62
4-Cl	10:1	65	Thien-2-yl	1:1	41
4-OH	3:1	42			

Scheme 16

4. Conclusion

After having examined extensive cyclocondensation and cycloaddition reactions described in the literature, it is necessary to return to the initial question. What is the role of ILs in these reactions? Now, it is clear that to adequately answer this question, the characteristics of each reaction must be considered. In this review, the main effects of the ionic liquids observed in cyclocondensation reactions were to improve the reaction yields and to shorten the reaction time. In cycloaddition reactions, besides the increase of yields and reduction of reaction time a better endo/exo selectivity was observed, in comparison to that found with molecular solvents. One can rationalize that ILs are good solvents for both cyclocondensation and cycloaddition reactions, due to the stabilization of TS of both reactions and, particularly, to the dual effect of catalyst-solvent and liquid-support in cyclocondensations and to the "solvophobic" effect in cycloaddition reactions. Moreover, considering the importance of the cyclocondensation and cycloadditon reactions, the main reactions in heterocyclic synthesis, the information presented here clearly illustrates the substantial advances achieved over the past decade in the use of ionic liquids as solvent in organic reactions. In addition, clear advantages of using ionic liquids, such as increased reaction rates and product yields and the possibility of avoiding complex workup procedures and of reusing these solvents have been demonstrated. Undeniably, ionic liquids enable more efficient reactions to take place when compared with molecular solvents. However, it is necessary to optimize both reactions in order to be able to make a truly accurate comparison. Large increases in reactivity and selectivity have been

achieved using this medium for homogeneous reactions, and in some cases, reactions have been shown to only work in the ionic environment and not in molecular solvents. In this chapter, we hope to have given a clear idea of the applicability of ionic liquids in cyclocondensation and cycloaddition reactions. We would like to conclude with an optimistic view for the future expansion of these reactions in ionic liquid media. This positive view comes from the certainty that the results reported here will be the beginning of a great advance in this promising field in the near future.

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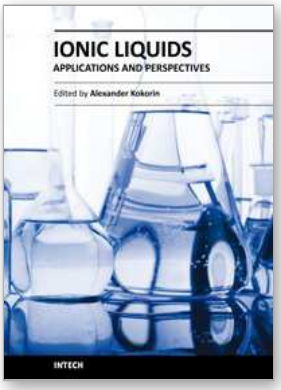

Ionic Liquids: Applications and Perspectives

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This book is the second in the series of publications in this field by this publisher, and contains a number of latest research developments on ionic liquids (ILs). This promising new area has received a lot of attention during the last 20 years. Readers will find 30 chapters collected in 6 sections on recent applications of ILs in polymer sciences, material chemistry, catalysis, nanotechnology, biotechnology and electrochemical applications. The authors of each chapter are scientists and technologists from different countries with strong expertise in their respective fields. You will be able to perceive a trend analysis and examine recent developments in different areas of ILs chemistry and technologies. The book should help in systematization of knowledges in ILs science, creation of new approaches in this field and further promotion of ILs technologies for the future.

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