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Ionic Liquids in Heterocyclic Synthesis

Marcos A. P. Martins,* Clarissa P. Frizzo, Dayse N. Moreira, Nilo Zanatta, and Helio G. Bonacorso

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria-RS, Brazil

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* Address correspondence to this author. Fax: +55 55 3220 8756. E-mail: mmartins@base.ufsm.br.

1. Introduction

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 can not 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 addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of significance for human and animal health. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models. A significant part of such biologically active compounds is composed of heterocycles. These compounds play a major part in biochemical processes and the side groups of the most typical and essential constituents of living cells. 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.[1] In fact, in the Comprehensive Medicinal Chemistry (CMC) database, more than 67% of the compounds listed contain heterocyclic rings, and nonaromatic heterocycles are twice as abundant as heteroaromatics.[2] 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. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, cyclocondensation reactions are among the most attractive methodologies for synthesizing heterocyclic compounds,[1] and the need for improved cyclocondensation reactions is evident.

Additionally, ionic liquids (ILs) have attracted increasing interest recently in the context of green organic synthesis. 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

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Marcos A. P. Martins was born in Carazinho, Rio Grande do Sul (RS) state, Brazil, in 1956 and in 1973 completed the elementary studies in Palmeira das Missões, in the same state. In 1977, he received his undergraduate degree in Chemistry from the Federal University of Santa Maria (RS), and in 1982, he received his Ph.D., under the direction of Professor R. Rittner, from the University of São Paulo, Brazil. In 1981, he moved to the Federal University of Santa Maria, where he is now a Titular Professor in Organic Chemistry. In 1987, he received a DAAD Postdoctoral Fellowship to work with Dr. G. Clar (*GTZ*), Dr. P. Fischer, and Professor F. Effenberger at Universität Stuttgart, Germany. In 1999, he received the FAPERGS award of the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul for his "outstanding contributions to chemistry". In the Federal University of Santa Maria, he now has leadership for the research group (three Research Associates, one Postdoctoral fellow, seven Ph.D. students, two M.S. students, and five undergraduate students) named NUQUIMHE, Núcleo de Química de Heterociclos, at the Department of Chemistry. His work has appeared in nearly 170 publications, reviews, and book chapters. Professor M. A. P. Martins is a researcher (1A) of the Brazilian National Research Council (CNPq) and serves as independent consultant to several cellulose and tobacco companies. His research interests are centered in heterocyclic chemistry with special emphasis in the development of novel building block precursors, synthetic methods, and use of ionic liquids in condensation reactions, "green procedures", and structural studies.

Clarissa Piccinin Frizzo was born in Ivorá, Rio Grande do Sul state, Brazil, in 1983. She received her B.S. in Pharmacia in 2005 from the Federal University of Santa Maria, Brazil. In 2007, she completed her M.S. degree at the same university under the supervision of Professor Marcos A. P. Martins, working with the synthesis of heterocycles and derivatives in ionic liquids. After that, she started her Ph.D. studies in the same group. Her research interests are focused on the design, preparation, and application of new methods to heterocyclic synthesis.

Dayse das Neves Moreira was born in Canguçu, Rio Grande do Sul state, Brazil, in 1984. She received her undergraduate degree in Chemistry from the Federal University of Pelotas, RS, in 2006, and in 2008, she received her M.S. degree from the Federal University of Santa Maria, RS, Brazil, working under the direction of Prof. Dr. Marcos A. P. Martins. Currently, she is a Ph.D. student with Prof. Dr. Marcos A. P. Martins in the Department of Chemistry of the Federal University of Santa Maria. Her major research interest is to develop new methodologies to synthesize heterocyclic compounds.

Nilo Zanatta was an undergraduate student in Chemistry at the Federal University of Santa Maria, Santa Maria, Brazil. He obtained his graduate degree at the Chemistry Institute of São Paulo University, São Paulo, Brazil, in 1981 under the supervision of Professor Roberto Rittner Neto. In 1982, he started his Ph.D. degree at the Chemistry Department of Syracuse University, Syracuse, NY, under the guidance of Professor George C. Levy, obtaining his Ph.D. degree at the beginning of 1986. His doctoral thesis focused on carbon-13 NMR assignments, structure, and dynamics of deoxyoligonucleotides. In 1986, he began his professional carrier as professor at the Chemistry Department of Federal University of Santa Maria, and now he is Associate Professor. Since 1986 he has been the director of the NMR laboratory and GC-MS facilities. His research activity is focused on heterocyclic chemistry, synthesis from halogenated enones, and structural studies thereof.

far beyond this boundary, showing their significant role in controlling reactions as solvent or catalysts.[3] Another feature of ionic liquids is their ability to be reused many times. Over the last few years, there have been several reviews published in which ionic liquids occupied a central theme. In these reviews, ionic liquids were considered in terms of (i) how ionic liquids might be useful in catalysis, not only for homogeneous and heterogeneous catalysis but for transition metal-mediated catalysis and organometallic reactions as well,[4c,d] (ii) their use as solvents in organic and bio-organic reactions,[5,6] and (iii) their reactivity.[7] However, there are few reviews available that deal with specific reactions in ionic liquids.[6,8] Although condensation reactions are among the reactions mentioned in some of these reviews, there has not yet been any review dealing with the employment of ionic liquids in heterocyclic synthesis from cyclocondensation reactions. In addition, some common heterocycles, for example, pyrazoles and isoxazoles, have not yet been synthesized from cyclocondensation reactions using ionic liquids.

Helio Gauze Bonacorso was born in Santa Maria, Brazil, in 1962. He studied chemistry at the Federal University of Santa Maria, Brazil, where he obtained his graduate degree in 1985 and his M.Sc. degree in 1988. Subsequently, he received his doctorate in 1993 from the University of Stuttgart, Germany, working within the group of Prof. Franz Effenberger and focused his doctoral thesis on the development of new methods for the synthesis of azepinones and condensed heterocyclic system derivatives. Since 1991, he has been Professor of Organic Chemistry of the Federal University of Santa Maria, Brazil, and during his research career, he has been the author or coauthor over 120 scientific papers, reviews, and book chapters. His current research interests include heterocyclic chemistry focused on the synthesis, structure determination, and biological evaluation of five-, six- and seven-membered trichloro(fluoro)methyl-substituted heterocycles.

Hence, the purpose of this review is to show the application of ionic liquids in heterocyclic syntheses from cyclocondensation reactions. This denotes a great deal of material to be covered; thus it was necessary to make some limitations to the scope of this review: (i) heterocycles obtained from cycloaddition reactions were excluded; (ii) only papers using ionic liquids as a solvent, liquid support, or catalyst have been considered, but biocatalyst reactions have been excluded; (iii) papers in which the reactivity of ionic liquids was evaluated have also been excluded.

The data shown in this review correspond to the period ending in March 2007. If some references are more recent, they correspond to results that were available to us during the elaboration of this manuscript. The data in the tables referred to as "the present study" are reported here for the first time. We have arranged the large volume of data in terms of the type of heterocycle formed, starting with three-, five-, six-, and seven-membered rings in the order of an increasing number of heteroatoms (that is, first with one heteroatom, two heteroatoms, and three heteroatoms) and the heteroatom order of N then O then S. Such systematic treatment may be useful in selecting the direction of further research.

2. Ionic Liquids

Ionic liquids are generally defined as liquid electrolytes composed entirely of ions, and occasionally a melting point criterion has been proposed to distinguish between molten salts and ionic liquids (mp < 100 °C). However, both molten salts and ionic liquids are better described as liquid compounds that display ionic−covalent crystalline structures.[9,10] Room-temperature ionic liquids (ILs) based on 1-alkyl-3-methylimidazolium salts were first reported in 1982 by Wilkes et al. as tetrachloroaluminates (first generation).[11] Replacement of this moisture-sensitive anion by the tetrafluoroborate ion and other anions led, in 1992, to air- and water-stable (second generation) ionic liquids,[12] which have since found increasing applications as reaction media for various kinds of organic reactions. At the onset of the new millennium, the concept of task-specific ionic liquids (third generation) was introduced by Davis.[13] These compounds are defined as ionic liquid in which the anion, cation, or both covalently incorporate a functional group (designed to endow them with particular properties, either physical or chemical or in terms of reactivity) as a part of the ion structure (Figure 1).[13,14]

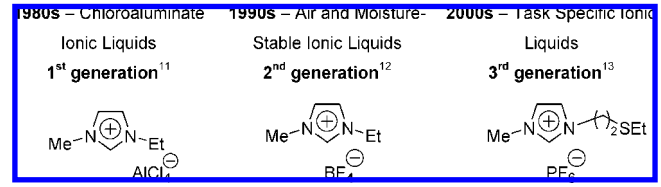


Figure 1. The three IL generations.

Suitably selected, many combinations of cations and anions allow the design of ionic liquids that meet all the requirements for the chemical reaction under study. This has gained them the alias of "designer solvents".[15] Properties such as solubility, density, refractive index, and viscosity can be adjusted to suit requirements simply by making changes to the structure of the anion, the cation, or both.[3,16,17]

2.1. Ionic Liquids in Organic Reactions

Many studies have reported on the application of ionic liquids in different areas and, in particular, on their use in organic reactions. On the other hand, there are a few reports that provide a clear discussion on questions such as "how do ionic liquids act in organic reactions?" or "are ionic liquids solvents, catalysts, or both?" Perhaps for the synthetic organic chemist, these questions are secondary, considering the significant improvement in products yields, reaction times, reaction work-up, etc., that they confer. However, we believe that the answer to (or at least the awareness of) these questions will allow the synthetic organic chemist to better plan the synthesis and thus improve results, making ionic liquids a strong tool in the area of organic synthesis.

"How ionic liquids act in organic reactions" is not clear and there has been and continues to be much controversy over this fact. Nevertheless, the authors agree that "the data on properties, such as dielectric constants, polarity, etc. are not sufficient to explain the solvent/catalyst effect of ionic liquids in organic transformations". Some have suggested that ionic liquids act as an organocatalyst.[18] One of the promising approaches to organocatalysis is through hydrogen-bonding interactions, and the results obtained with some ionic liquids have confirmed this statement and demonstrate their potential to have a huge impact on organocatalysis. On the other hand, Welton[4b,d] 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, many studies on the properties of the solvents of the ionic liquids have been carried out. There is indeed a great amount of data on properties such as dielectric constants and polarity that have been obtained from different methods. Each author argues

Table 1. Kamlet−Taft Solvent Parameters for Several ILs

	E_T[a]	π^*	α	β	ref
[BMIM][BF_4]	0.67	1.047	0.627	0.376	24
[BMIM][PF_6]	0.669	1.032	0.634	0.207	24
[BMIM][TfO]	0.656	1.006	0.625	0.464	24
[BMIM][Tf_2N]	0.644	0.984	0.617	0.243	24
[OMIM][PF_6]	0.633				22b
ethanol	0.65				5a

[a] E_T = 28592/(the wavelength maximum of the lowest energy $\pi-\pi^*$ absorption band of the zwitterionic Richardt's dyes).[5a]

that his method to determine some properties for a particular substrate or solvent is the best. For example, some studies indicate that ionic liquids have polarities similar to those of short-chain alcohols and other polar, aprotic solvents (DMSO or DMF) and that their polarity is intermediate between that of water and chlorinated organic solvents, varying in accordance with the nature of the its components.[3,19] Others report that they exhibit solvent strengths as great as or greater than the most polar aprotic solvent (acetonitrile).[20] Still others have classified them as solvents of moderate polarity.[21]

2.2. Ionic Liquids as Solvent

Considering that the majority of studies in the literature show ionic liquids in a molar ratio ≥1.0 in relation to substrate, we believe that the best approach to answering the above-mentioned questions is considering the ionic liquid as a solvent. Solvent polarity is the most commonly used solvent classification. The simplest qualitative definition is that a polar solvent is one that will dissolve and stabilize dipolar or charged solutes. It is widely thought, though yet to be generally demonstrated, that under this definition, ionic liquids will be highly polar solvents. Moreover, attempts have been made to develop empirical solvent polarity scales of ionic liquids as a means of helping to explain differences in solvent-mediated reaction pathways, reaction yields, synthesis product ratios, chromatographic retention, and extraction coefficients. More than 20 years ago, Abboud, Kamlet, and Taft proposed an interesting system to separate nonspecific effects of the local electrical fields from hydrogen-bonding effects. Based on the comparison of the effects on the UV−visible spectra of sets of closely related dyes, they evaluated some properties, in particular, dipolarity or polarizability (π^*), H-bond basicity (β), and H-bond acidity (α).[22] Different investigations of solvent−solute interactions in ionic liquids using solvatochromic dyes have been reported.[20,23] Recently, Crowhurst et al.[24] applied the Abboud−Kamlet−Taft method using three solvatochromic dyes (Richardt's[25] dye, *N*,*N*-diethyl-4-nitroaniline, and 4-aniline) to determine the solvent parameters π^*, β, and α of imidazolium ILs (Table 1). The π^* values found by Crowhurst et al. for the investigated ILs indicate that the dipolarity or polarizability of these salts is higher than that of alkyl chain alcohols. Although differences between the ILs are small, both the cation and the anion affect this parameter. At variance, the H-bond basicity of the examined ILs covers a large range, from a similar value to that of acetonitrile to lower β-values. The anion nature dominates this parameter. Finally, the H-bond acidity is determined by the cation, even if a smaller anion effect is present. In particular, it has been suggested that the α values are controlled by the ability of the cation to act as an H-bond acceptor; a strong anion−cation interaction reduces the ability of the cation to hydrogen bond with the substrate. The acidity of the investigate ILs is generally less than those of water and most short-chain alcohols but greater than those of many organic solvents, such as aniline.

The solvent properties of the ionic liquids have also been investigated using chromatographic techniques.[26−28] It was generally found that the ionic liquids could be considered to be polar phases with the solvent properties being largely determined by the ability of the salt to act as a hydrogen-bond donor or acceptor. Anderson et al. measure solvent properties of ionic liquids[29] using the GC retention times of a range of probe solutes on a variety of columns using ionic liquids as the stationary phases; they were able to make some general statements as to how the ionic liquids were behaving. The ionic liquids were interacting with solute via high dipolar and dispersion forces and also acting as strong hydrogen bond bases. The dipolar forces and hydrogen bond basicity varied with the different ionic liquids, whereas the dispersion forces were nearly constant for all of the ionic liquids studied. The hydrogen bond basicity was dominated by the choice of anion. When hydrogen bond acidity was observed, it arose from the cation of the ionic liquid, although the anion also greatly influenced this property.

Most simple molecular solvents (hexane, for example) are limited in the number and types of solvation interactions possible with dissolved molecules. More complex solvents with additional functional groups can produce additional interactions with dissolved molecules. Ionic liquids are among the most complex solvents. Given their structure and the diversity of their functionality, they are capable of most type of interactions (e.g., dispersive, $\pi-\pi$, n−π, hydrogen-bonding, dipolar, and ionic or charge−charge). In every solution, there may be a number of differences (in terms of type and strength) and often simultaneous solute−solvent interactions. The various single-parameter polarity scales are essentially weighted averages of all possible solute−solvent interactions. Thus, it is not surprising that these averages are similar for any class of solvents and that they do not adequately explain many experimental observations. Since ionic liquids are much more complex solvent systems capable of undergoing many types of interactions, characterizing them with a single polarity term fails to encompass the broad spectrum of types and the magnitude of individual interactions that make each ionic liquid unique. Ionic liquids exhibit multiple behaviors, which explains why many ionic liquids act as polar solvents in organic reactions containing polar molecules and as less polar solvents in the presence of less polar molecules.[29] Also, the well-established scenarios for describing dipolar interactions in molecular liquids are not easily transferred to ionic liquids because the net charges of the ions create a fundamentally different environment with partial charge ordering and screening of dipole−dipole interactions by the sea of surrounding ions. The presence of charged species adds new degrees of freedom in the mix of interactions. In this case, the concept of polarity may even require a careful rethinking of the fundamental nature of solvation.[30]

Clearly, a single parameter of "polarity", "solvent strength", or "interaction" is not sufficient to explain the variation in experimental results in 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,

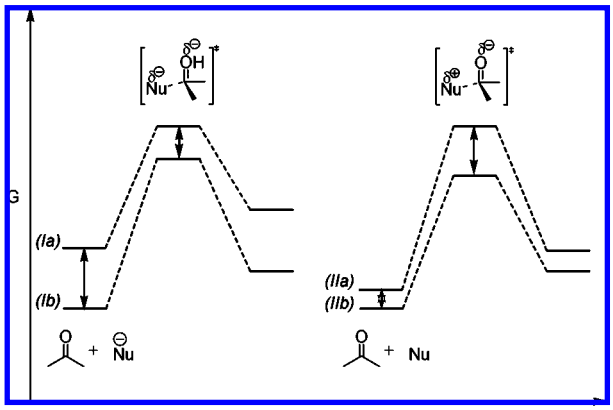


Figure 2. Schematic Gibbs energy diagram for a general nucleophilic addition to carbonyl carbon: (a) nonpolar solvents; (b) polar solvents.

such as carbocations or carbanions, and activated complexes, which could become more stable and long-lived in this media.[5b] 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 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[31] 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 2). 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.

2.3. Ionic Liquids as Catalyst

An ionic liquid can be useful if the cation or anion of the ionic liquid can act as a catalyst, catalyst activator, or cocatalyst for a reaction. In some of the more recent examples found in the literature, the ionic liquid is deliberately prepared so that one of the ions serves as the catalyst for the reaction.[32,33] Functionalized ionic liquids that are able to act as catalysts, particularly imidazolium salts containing anionic selenium species, $[SeO_3Me]^{\ominus}$, have been prepared.[34] These salts have been used as selenium catalysts for the oxidative carbonylation of anilines. Analogously, ionic liquids bearing acid counteranions ($[HSO_4]^{\ominus}$ and $[H_2PO_4]^{\ominus}$) have been used in catalyzed esterifications as recyclable reaction media.[35] Similar results have also been obtained using zwitterionic ionic liquids bearing a pendant sulfonate group, which can be converted into corresponding Brønsted acid ionic liquids, by reaction with an equimolar amount of an acid that has a sufficiently low pK_a (TsOH, TfOH).[36] Ionic liquids, containing the function SO_3H, have recently been employed in the oligomerization of various alkenes to produce branched alkene derivatives with high conversions and excellent selectivity.[37] Protonated ionic liquids have been synthesized by direct neutralization of alkylimidazoles, imidazoles, and other amines with acids and their physical properties (thermal stability, conductance, viscosity) are currently under investigation. However, NMR studies seem to indicate, at least in the case of 1-methylimidazolinium bromide, that the nitrogen proton is not labile, and, therefore, this salt cannot be viewed as a conventional Brønsted acid. Brønsted-basic ionic liquids have also described as catalysts to organic reactions, for example, Ranu and Banerjee demostrated the use of a tailor-made, task-specific, and stable ionic liquid [BMIM][OH] as basic catalyst for Michel addition.[38]

On the other hand, the asymmetric synthesis of ionic liquids is still at a preliminary stage. Chiral ionic liquids, for example, have been synthesized, and their use in asymmetric synthesis is under investigation.[39–42] Finally, ionic liquids have been little used as catalysts, and their behavior as such is not well established. One explanation is that it is highly probable that ionic liquids act mainly as solvents in all cases.

2.4. The Role of Ionic Liquids in Specific Reactions

In light of the information addressed above, it is clear that the role of ionic liquids in organic reactions has been investigated in a general manner and that more detailed studies have been limited to certain reactions. The most widely studied reaction in which ionic liquids can be considered solvents is the nucleophilic substitution reaction. Investigations of this reaction have used ionic liquids as solvents for a wide range of chemical processes, both stoichiometric and catalytic. 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.[4] 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.[5] This is the case of the nucleophilic alkylation of nitrogen or oxygen atoms by haloalkanes in the presence of a base, which involves the preformation of an anionic intermediate. In $[BMIM][PF_6]$, the alkylation of indole or naphthol occurs with similar reaction rates compared with organic polar solvents but with very good regioselectivity.[43] To understand how such effects may arise, a range of relatively simple and well-understood reactions (S_N2) was studied in a variety of ionic liquids. The first thing that became apparent from the results reported was that not all ionic liquids were the same, that is, one cannot simply take a conventional organic reaction and replace the solvent with a single ionic liquid and then expect the result to be the same as what would be achieved in any other ionic liquid. Thus, by the same token, the results validate the claims[5a,44] that ionic liquids can be tailor-made for a given reaction. It is possible to imagine that ionic liquids could be produced with the ideal combination of cation and anion for any given reaction. Although the studies only dealt with S_N2 reactions, it is possible to generally state that when using ionic liquids for reactions of highly associating anions such as halides, reaction rates will probably be greater in ionic liquids composed of the least coordinating cations (poor hydrogen bond acids); that is, the rate of reaction is affected by H-bonding ability and ion pairing of IL. In fact, the relative rates of reaction can be explained (and predicted) by the classical Hughes−Ingold approach to examining solvent effects on organic reactions. The H-bonding ability and ion pairing of ionic liquid have been also used to explain

the increase of reactivity and selectivity of eletrophilic additions. In molecular solvents, the nature of the ionic intermediate is not dependent on the properties of the solvent; in contrast, the lifetime of the ionic intermediate depends on the solvent. Probably also in ILs, the nature of the intermediates is not affected by the medium, whereas the latter can affect the lifetime of these intermediates, affecting the stability of the ionic intermediate or modifying the nucleophilicity of the attack anion. Furthermore, it can also affect the *syn*/*anti* ratio, decreasing the rate of isomerization of the ionic intermediates through rotation around the C−C bond.

In reaction of electron transfer, the enhancement of reactivity has been attributed to the effect of cation−anion association and the presence of cavities in the ILs. The electron transfer reaction may, however, be affected by the solvent also through the change in the energy of solvation of the charged species. It has been suggested that the highly ordered structure of these salts may contain voids, and these voids can accommodate small solute molecules. Thus, the presence of voids and the ability of small molecules to move within them have also been proposed recently to explain the reactivity of hydrogen radical ($H^{\bullet}$) atoms with aromatic solutes in ILs.[45–47]

In the case of Diels−Alder reactions, there is evidence of the importance of the cohesive energy density together with the hydrogen-bonding donor capacity to the reaction rate.[48–51] The cohesive energy density essentially should quantify solvophobicity, underlining the importance of the hydrophobic interactions in rationalizing the effect of solvents such as water on Diels−Alder reactions. The *endo* selectivity in ILs is therefore explained considering the ability of the cation of the IL to act as a to hydrogen bond donor, a property that is modulated by the abiblity of the counteranion to act as an hydrogen bond acceptor. An illustration of these effects of the ionic liquid has been shown by the examination of water solvation in ionic liquids using simulation[52] and vibrational spectroscopy.[53] A clear dependence on the dispersion of water in ionic liquids with respect to its concentration has been established. At low concentrations, the water is molecularly dispersed, whereas at higher concentrations, aggregated water is also present. In contrast, in mixtures of water in alcohols, for example, the liquid phase separates on a microscopic scale to form hydrophobic regions and hydrophilic regions.[54] This detailed description has provided an explanation as to why some "wet" ionic liquids can hydrolytically stabilize, for example, unstable solutes.[55]

Another type of reaction that has been widely studied in ionic liquids is the catalyst reaction.[4a,b] Ionic liquids have shown significant advantages over conventional solvents for homogeneously catalyzed reactions.[4c] In these cases, the ionic liquid can be used in "biphasic catalysis" or the catalyst can be entrapped or "immobilized" allowing extraction or distillation of the organic product, and the ionic liquid/catalyst system can be reused. Reactions of transition metal catalysis in ionic liquids with weakly coordinating anions (such as $[(CF_3SO_2)_2N]^{\ominus}$, $[BF_4]^{\ominus}$, or $[PF_6]^{\ominus}$ under anhydrous conditions) and cations, which do not coordinate to the catalyst themselves or form species that coordinate to the catalyst under the reaction conditions used, can be considered simple solvents. However, the chemical inertness of these ionic liquids does not necessarily denote that the reactivity of a transition metal catalyst dissolved in an ionic liquid is equal to the reactivity observed in common organic solvents. In order to achieve sufficient solubility of the metal complex, a solvent of higher polarity is required, and this may compete with the substrate for the coordination sites at the catalytic center. Consequently, the use of an inert, weakly coordinating ionic liquid in these cases can result in a clear enhancement of catalytic activity, since some ionic liquids are known to combine high solvation power for polar catalyst complexes (polarity) with weak coordination (nucleophilicity).[4a] Ionic liquids formed by treatment of a halide salt with a Lewis acid (such as chloroaluminate or chlorostannate melts) generally act both as solvent and as cocatalyst in transition metal catalysis. Both the cation and the anion of an ionic liquid can act as a ligand or ligand precursor for a transition metal complex dissolved in the ionic liquid.[4c,d]

There are several types of reactions in which the pronounced effect of ILs has been observed, but more complete studies of these reactions are yet to be made. The following reactions are of consequence for this review: (i) Michael additions;[56–58] (ii) cross-condensation of carbonyl compounds with derivatives of cyanoacetic acid;[59] (iii) 1,4-conjugate addition of unmodified aldehyde;[60,61] (iv) Baylis−Hillman reaction;[62–64] (v) cross-coupling between aldehydes and allylic alcohols.[65]

2.5. Ionic Liquids Presented in This Review

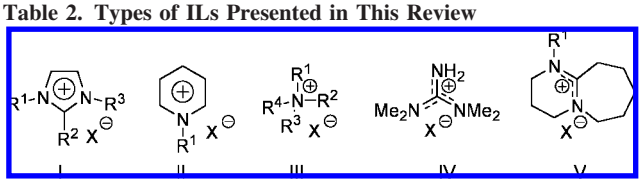
In view of previous studies on the effect of ionic liquids in certain reactions, we believe it to be very important to evaluate the profile of ionic liquids in cyclocondensation reactions. Indeed, the studies on reactions of S_N2 have shown that not all ionic liquids are the same and that one cannot simply take a conventional organic reaction, replace the solvent with a single ionic liquid, and then expect the result to be the same as would be achieved in any other ionic liquid. Therefore, we intend to investigate whether it is possible to generalize the effect of ionic liquids in cyclocondensation reactions. For this propose, we emphasize that the ionic liquids used in heterocyclic synthesis from cyclocondensation reactions have been classified into five main categories based on their structures (I−V, Table 2) and that the majority of the studies published (>80%) used ionic liquids based on the imidazolinium cation (I). Another important finding is that, as expected, ca. 80% of the authors used a molar ratio of IL ≥ 1.0 in relation to the substrate, ca. 10% use a molar ratio ≤0.5 in relation to the substrate, and in ca. 10% of the papers, the authors did not disclose the molar ratio used.

3. 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).[66]

In this review, the synthesis of series of three-, five-, six-, and seven-membered heterocyclic rings obtained from cyclocondensation reactions will be described. These reactions were carried out with different numbers of components, as summarized in the Figure 3. The functional groups contained in each component can react as electrophile (E_1, E_2 and E_3) or nucleophile (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

Table 2. Types of ILs Presented in This Review



ionic liquid	X	R^1	R^3	R^2	R^4
		I			
2-AEMIM	PF_6	2-aminoethyl	Me		
2-HYDEMIM	BF_4	Me	2-hydroxyethyl		
2-HYDEMIM	PF_6	Me	2-hydroxyethyl		
BBIM	BF_4	Bu	Bu		
BDMIM	Tf_2N	Me	Bu	Me	
BDMIM	$PFBuSO_3$	Me	Bu	Me	
BDMIM	PF_6	Me	Bu	Me	
BMIM	Br	Me	Bu		
BMIM	Cl	Me	Bu		
BMIM	BF_4	Me	Bu		
BMIM	PF_6	Me	Bu		
BMIM	OH	Me	Bu		
DMIM	BF_4	Me	Decyl		
EMIM	CF_3SO_3	Me	Et		
HBIM	BF_4	H	Bu		
HeMIM	BF_4	Me	Heptyl		
HMIM	Tfa	H	Me		
PsMIm	PF_6	Me	polystyrene		
		II			
BPy	BF_4	Bu			
NBP	$FeCl_4$	Bu			
		III			
Bu_4N	Br	Bu	Bu	Bu	Bu
Bu_4N	Cl	Bu	Bu	Bu	Bu
$EtNH_3$	NO_3	Et	H	H	H
		IV			
TMG	Tfa				
		V			
pyrimido[1,2-*a*] azepin-1-ium[a]	CF_3SO_3	Me			
pyrimido[1,2-*a*] azepin-1-ium[a]	CF_3SO_3	Et			

[a] 1,8-Diazabicyclo[5.4.0]-7-undecenium.

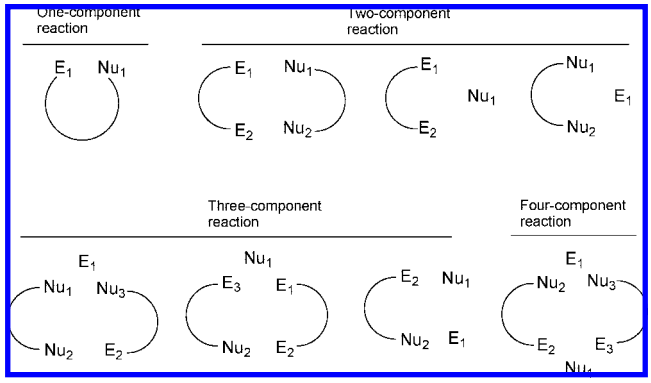


Figure 3. Number of components in the cyclocondensation reactions discussed in the review.

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.

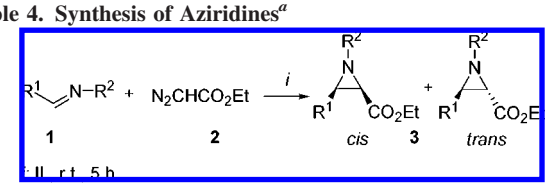
In Table 3 are shown the reaction type and building blocks that are found in cyclocondensation reactions described in this review. In the first column are ilustrate the reactions type in accordance with the components number. In the second column are explained the number of components, and in the third column are demonstrated the building blocks of the reactions. So, for example, the representation [3 + 2] → [CCC + NN] indicated that the heterocycle was formed by two building blocks, one of these building blocks possess three atoms ([CCC]) and the other posess two atoms ([NN]). In the last column are listed 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 one carbon−heteroatom and one carbon−carbon bond was observed. 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.

Table 3. Reaction Types and Building Blocks of Cyclocondensation Reactions

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]	quinazolinone
[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

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 of α,β-unsaturated systems or a heteroatom nucleophilic substitution into mono- and dihalo-

Table 4. Synthesis of Aziridines[a]



entry	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
6	[BMIM][PF_6]	4-Me-Ph	Ph	83, *cis* only
7	[BMIM][PF_6]	4-Me-Ph	4-Me-Ph	91, *cis* only
8	[BMIM][PF_6]	2-MeO-Ph	Ph	85, *cis* only
9	[BMIM][PF_6]	4-Cl-Ph	Ph	98, *cis* only
10	[BMIM][PF_6]	2-Cl-Ph	Ph	97, *cis* only
11	[BMIM][PF_6]	4-NO_2-Ph	Ph	98, *cis*/*trans* 34:1
12	[BMIM][PF_6]	4-Br-Ph	Ph	98, *cis* only

[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] Performed with 1.0 mmol of imine and 0.5 mmol of EDA. [d] Performed with 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] Performed with 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.

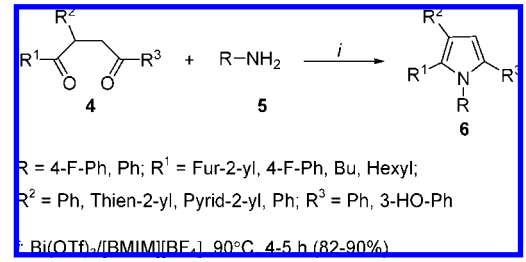
substituted carbons or acetal and orthoester carbons. The formation of carbon−carbon bonds, in general, involves a nucleophilic addition (in most cases, with a second step elimination reaction) of a carbon atom nucleophile (carbonyl α-carbon) to a carbonyl (imine or nitrile) carbon atom or to the β-carbon of α,β-unsaturated systems.

4. Synthesis of Three-Membered Heterocycles

4.1. Aziridines

The aziridine functionality, also called the azaethylene or ethylenimine unit, represents one of the most valuable three-membered ring systems in modern synthetic chemistry because of its widely recognized versatility as a significant building block for chemical bond elaborations and functional group transformations. Its powerful synthetic utility has been demonstrated by an overwhelming amount of documentation on methodologies for the preparation of aziridine, especially those including asymmetric approaches. It also has a broad spectrum of applications in other syntheses.[67] There is only one route for obtaining aziridines using ionic liquids described in the literature. Xia et al.[68] described the synthesis of aziridines **3**using ionic liquids from the reaction of imines **1** and EDA **2** (Table 4). 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 related by the authors explain the results of entries 4 and 5 in Table 4, where a catalytic amount (0.1 mmol) of ionic liquid was dissolved in a co-organic solvents. As summarized in Table 4, 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% to 91% yield). The formation of

Scheme 1



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·OEt_2) in molecular solvent such as hexane, in which the yield obtained was 93% after 15 h at 25 °C.[69]

5. Synthesis of Five-Membered Heterocycles

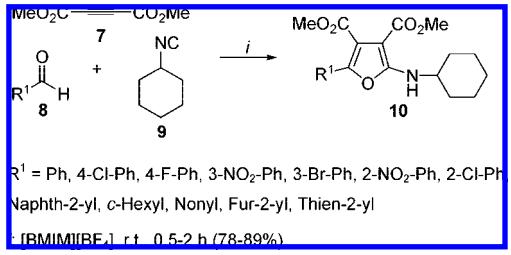
5.1. Pyrroles

Pyrroles are an important class of heterocyclic compounds and are widely used in synthetic organic chemistry and materials science. Due to their distinctive properties, extensive investigations have been made to develop preparative methods for substituted pyrroles. In general, 1,2,3,4-tetra-substituted pyrroles have been prepared by Knorr reactions,[70] Hantzsch pyrrole synthesis,[71] or the 1,3-dipole addition of azomethyne ylides with alkynes.[72] Classical methods to access pyrrole derivatives also involve condensation reactions of 1,4-dicarbonyl reactants.[73] Recently, this method of obtaining pyrrole derivatives was adapted in a methodology using ionic liquids, where [BMIM][BF_4] was employed[74] in the condensation reaction of 1,4-dicarbonyl reactants **4** and primary amines **5** as shown in Scheme 1. Although this route to pyrroles **6** is widely exploited, the publication reported above is the only one in the literature that demonstrates the attainment of this heterocycle using ionic liquids. In the procedure, the ionic liquid was used in a molar ratio of 1:16 (reactant/IL), and it was recovered and reused four times with only a gradual decrease in activity (87%, 85%, 81%, and 76% yields). The authors cited that the reaction proceeded smoothly not only in ionic liquids but also in refluxing toluene in the presence of 5 mol % $Bi(OTf)_3$.The use of $Bi(OTf)_3$/[BMIM][BF_4] was found to be the ideal catalytic system for these condensations. Moreover, the recovery and reuse of $Bi(OTf)_3$was especially easy in ionic liquids compared with that in toluene. Although the procedure in ionic liquid included a catalyst, $Bi(OTf)_3$, it was considered more convenient and faster than those iodine-catalyzed reactions using molecular solvents such as THF or dichloromethane (20 h at rt).[75]

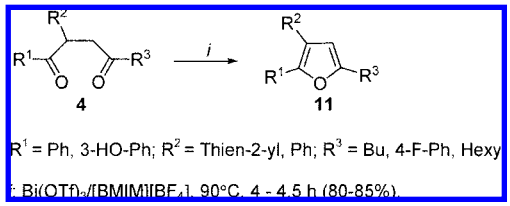
5.2. Furans

Furans, another class of heterocycles, are versatile pharmacophores possessing a variety of biological activities.[76] The furan moiety is a core structure of many alkaloids, such as kallolides and cembranolides.[76] Furans are generally prepared from 1,4-dicarbonyl compounds using acid catalysts. Strong acids, such as montmorillonite KSF, and basic reactants, including TsCl/DBU, have been used for their synthesis.[76] Furans can also be prepared through a multi-component reaction in a one-pot operation. However, the synthesis of furans remains a challenge for synthetic chemists

Scheme 2



Scheme 3

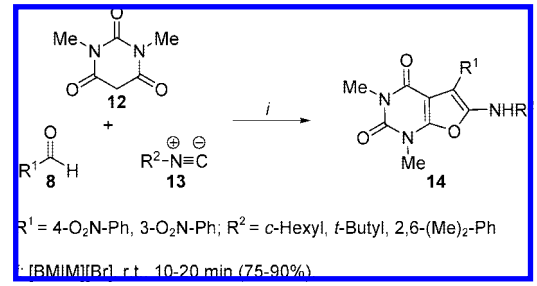


because of their sensitivity to acids. Taking this into account, Yadav et al.[77] developed a synthetic route using ionic liquids to synthesize 2-aminofurans **10**. These furan derivatives **10** resulted from the multicomponent coupling of aldehydes **8**, dimethyl acetylenedicarboxylate **7**, and cyclohexyl isocyanide **9** (Scheme 2). The use of [BMIM][BF_4] in a molar ratio of 1:16 (reactant/IL) at room temperature afforded products **10** in high yields and a short time reaction without the need for a catalyst. In addition, the ionic liquid was easily recovered after the reaction and reused several times without loss of activity, even after the fourth reuse. This reaction probably proceeded via the formation of a zwitterionic intermediate from DMAD and **9**, which underwent addition on the carbon−oxygen double bond and subsequently resulted in the formation of **10**. The anticipated zwitterionic intermediate exhibited enhanced reactivity in the ionic liquid thereby reducing the reaction times and improving the yields significantly.[77] The use of molecular solvents such as acetonitrile and tetrahydrofuran gave poor yields (30−65%) in this reaction even under refluxing conditions for long reaction times (8−12 h).

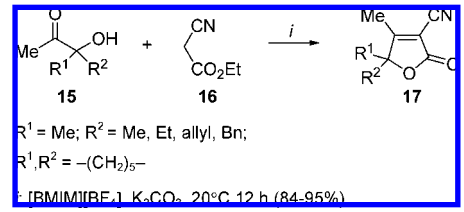
Yadav et al.[74] also applied ionic liquids to synthesize furans **11** from **4** using 5 mol % $Bi(OTf)_3$ immobilized in air- and moisture-stable [BMIM][BF_4] (Scheme 3). Various substituted 1,4-dicarbonyl compounds **4** underwent smooth cyclization to give the corresponding trisubstituted furans **11**, as shown in Scheme 3. In this procedure, the ionic liquid was used as solvent, and it was recovered and reused four times with only a gradual decrease in activity (87%, 85%, 81%, and 76% yields). In the absence of bismuth(III) triflate, no cyclization was observed in the ionic liquid. In this paper, as in the pyrrole synthesis, the authors observed that there were formations of furans **11** in refluxing toluene in the presence of the same catalytic amount of bismuth(III) triflate. However, the authors concluded that the ideal catalytic system is 5 mol % $Bi(OTf)_3$/[BMIM][BF_4], because the recovery and reuse of the catalyst was easier in ionic liquids than it was in toluene. Even though these routes needed the catalyst, they could be considered more convenient than those described in the literature, which involve a large quantity of trifluoride etherate (80 mL) and a long reaction time (24 h).[78]

The synthesis of furopyrimidines has received little attention, and only a few procedures have been reported in the literature.[79,80] In the continuation of their studies on the development of new routes for the synthesis of organic

Scheme 4



Scheme 5



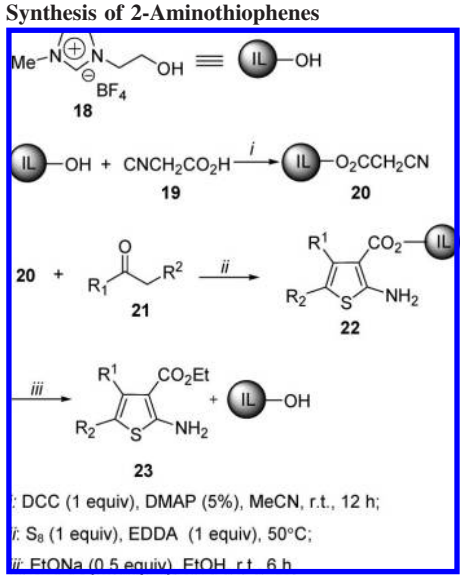
compounds using ionic liquids[81] and in their interest in isocyanide-based MCRs,[82] Shaabani et al.[83] developed a synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **14** via the three-component condensation of *N*,*N*′-dimethylbarbituric acid **12**, aldehydes **8**, and alkyl or aryl isocyanides **13** in [BMIM][Br] in a molar ratio of 1:1 (reactant/IL) at room temperature (Scheme 4). To explore the scope and limitations of this reaction, Shaabani et al.studied the reactions of **12** and **13** with **8** bearing either electron-releasing or electron-withdrawing substituents. It was found that the presence of an electron-withdrawing functional group was necessary for the formation of the desired product, because when **8** was carrying electron-releasing groups (such as 4-Me or 4-OMe) the products were obtained in poor yields. To illustrate the need for [BMIM][Br], the reaction of 4-nitrobenzaldehyde, **12**, and cyclohexyl isocyanide **13** was studied in the absence of [BMIM][Br]. The yield of the product was only 60% at room temperature after 24 h. This clearly demonstrates that [BMIM][Br] is an important component of the reaction.

Another interesting class of furan derivatives is that of substituted furan-2-ones (or butenolides). The butenolide moiety is an important framework present in a number of biologically active compounds.[84] The synthesis of this kind of compound involves a base-catalyzed transesterification, followed by a Knoevenagel reaction favored by the Thorpe−Ingold effect.[85] Villemin et al.[86] investigated the synthesis of butenolides **17** using ionic liquids with ethyl cyanoacetate **16**, and several α-hydroxyketones **15** (Scheme 5). Different ionic liquids were tested before retaining [BMIM][BF_4] for its easy preparation and convenience. The ionic liquid was used in a molar ratio of 1:1.5 (reactant/IL) and was recovered and reused three times for the same reaction without a loss of yield (94%, 94%, 93%). The butenolides **17** were obtained using [BMIM][BF_4] with better yields than previously reported in the literature in molecular solvents (63%−67%).[87,88]

5.3. Thiophenes

Thiophenes are yet another class of important and well-studied heterocycles.[89] The interest in this kind of heterocycle has spread from early dye chemistry[90] to modern drug design,[91] biodiagnostics,[92] electronic and electro-optical devices,[93]conductivity-based sensors,[94] and self-assembled

Table 5. Synthesis of 2-Aminothiophenes



entry[a]	R^1	R^2	time (h)	yield (%)
1	Me	Me	6	75
2	Et	Me	6	77
3	Me	CO_2Et	6	70
4	Me	CO_2Me	6	69
5	H	Me	5	68
6	H	Et	5	67
7		$-(CH_2)_4-$	3	91
8		$-(CH_2)_4-$	3	89
9		$-(CH_2)_4-$	3	88
10		$-(CH_2)_3-$	5	83

[a] Data refers to step ii.

superstructures.[95] The general synthetic approach to such compounds either involves functionalization at the α- and β-positions to the sulfur atom of the preconstructed thiophene nucleus[96] or the construction of a thiophene ring from appropriately substituted open chain precursors.[97] The latter has become more attractive for its general applicability in the attainment of more complicated substitution patterns.[98] Gewald et al.[99] developed the synthesis of 2-aminothiophenes from the multicomponent condensation of ketones or aldehydes, cyanoacetate, and elemental sulfur. Many modifications of the Gewald reaction have been developed recently, such as using a solid support,[100] microwave irradiation,[101] heterogenous catalysis,[102] and Lewis acid catalysis.[103] Hu et al.[104] reported the synthesis of 2-aminothiophenes **23** by the Gewald reaction using ionic liquids as soluble support (Table 5). As can be seen, the reaction of an ionic liquid with a minor excess of cyanoacetic acid (1.2 equiv) **19** in the presence of DCC and a catalytic amount of DMAP in dry MeCN produced the functionalized ionic liquid phase bond through ester linkage in **20**. The reactants, ketones or aldehydes **21**, S_8, and EDDA, were then added. Finally, treatment of the corresponding products **22** with NaOEt in ethanol resulted in a very efficient cleavage of ionic liquid support to provide the 2-aminothiophenes **23** with high purity and without the need for chromatographic purification. Compared with 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 byproducts. As liquid support, the ionic liquid was used in a molar ratio of 1:1 (reactant/IL). The ionic liquid phase was recovered and reused twice with no appreciable decrease in yields and reaction rates. The attainment of thiophenes **23** using molecular solvents such as THF entailed a painstaking, tedious, and long procedure with the addition of $TiCl_4$ at 0 °C followed by pyridine and stirring overnight at room temperature.[105] The yields obtained in THF/$TiCl_4$ were similar to those found in ionic liquid.

Scheme 6

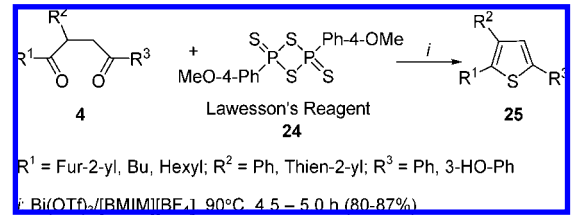
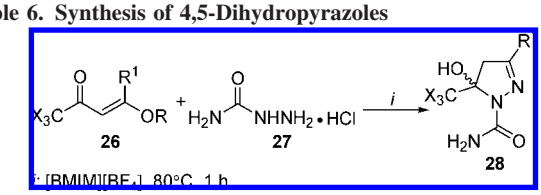


Table 6. Synthesis of 4,5-Dihydropyrazoles



entry	R	R^1	X	yields (%)[a] [conventional method]	yields (%) [the present study]
1	Et	H	Cl	65	78
2	Me	Me	Cl	71	73
3	Me	Ph	Cl	89	86
4	Et	H	F	73	85
5	Me	Me	F	65	80
6	Me	Ph	F		80

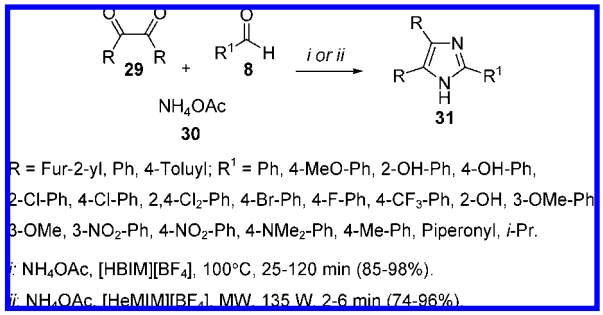
[a] Reflux (EtOH), 16 h.[108d]

Yadav et al.[74] exploited the applicability of ionic liquids in a one-pot synthesis of substituted thiophenes **25**. The reaction from 1,4-dicarbonyl compounds **4** and Lawesson's reagent **24** was conducted using $Bi(OTf)_3$ (Scheme 6). Similar to the synthesis of pyrroles **6** and furans **11**, ionic liquid was used as solvent, and it was recovered and reused four times with only a gradual decrease in activity (87%, 85%, 81%, and 76% yields). In this simple synthesis, as was also shown for pyrroles **6**[74] and furans **11**,[74] the catalytic system, 5 mol % $Bi(OTf)_3$/[BMIM][BF_4], was considered the ideal catalyst compared with toluene.

5.4. Pyrazoles

The vast majority of medicinal drugs or agrochemicals incorporate at least one heterocyclic ring in their molecular structure. Among these, there are many halo-substituted 1*H*-pyrazoles and derivatives known to exhibit important biological activities.[106] The synthesis of pyrazoles by the so-called [3 + 2] atom fragments has been relatively well investigated. In this method, β-diketones or their derivatives, such as the three-atom fragment, are condensed with hydrazine and its derivatives (the two-atom fragment) to close the five-membered ring.[107] Martins et al. have developed a method for the synthesis of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones, important halogen-containing building blocks for heterocyclic preparations.[108a,b] These authors have published the synthesis of a series of halogen-containing 4,5-dihydropyrazoles.[108c,d] Thus, considering the importance of this class of compounds, we reported here for the first time the synthesis of 4,5-dihydropyrazoles **28** using ionic liquids (Table 6).[108e] 4,5-Dihydropyrazoles **28** were obtained from the reaction of enones **26** with hydrazine **27** in the presence

Scheme 7



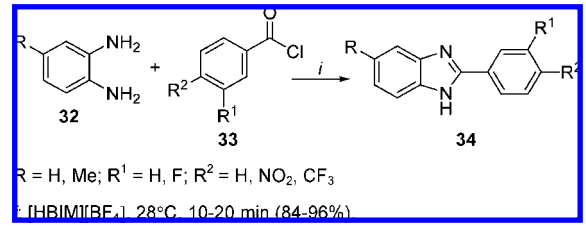
of equimolar quantities of ionic liquid. As illustrated in Table 6, these reactions presented some advantages over the same experiment carried out in the absence of an ionic liquid.[108] The yields were higher and the reaction time was shorter in comparison to those for the conventional method performed in absence of pyridine.

5.5. Imidazoles

Compounds with an imidazole ring system have many pharmacological properties and can play important roles in biochemical processes.[109] Several methods of imidazole synthesis can be found in the literature, including hetero-Cope rearrangement,[110] four-component condensation of arylglyoxals, the combination of primary amines, carboxylic acids, and isocyanides on Wang resin,[111] the reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate,[112] the use of 1,2-amino alcohols in the presence of PCl_5[113] and, finally, the combination of diketones, aldehydes, amines, and ammonium acetate in one of five possible media—phosphoric acid,[114] acetic acid,[115] acetic acid or H_2SO_4 with organocatalysts,[116] or DMSO.[117] There have been reports of several assisted syntheses of imidazoles from 1,2-diketones and aldehydes in the presence of a variety of catalysts.[117–123] Siddiqui et al.[124] described a one-pot condensation of 1,2-diketones **29**, aldehyde aromatics **8**, and ammonium acetate **30** that afforded a diverse array of 2,4,5-triarylimidazoles **31** in excellent isolated yields in the absence of any catalyst (Scheme 7). The authors proposed that [HBIM][BF_4] promoted this reaction by virtue of the inherent Brønsted acidity conferred by its most acid hydrogen, N−H (chemical shift $\delta = 14.6$). This would make the ionic liquids capable of bonding with carbonyl oxygen, increasing the reactivity of the parent carbonyl compounds. The ionic liquid was used in a molar ratio of 1:1 (reactant/IL), and it was recovered and reused three times without any loss of activity. A typical reaction of **29** with 4-anisaldehyde under similar conditions in the absence of a catalyst using molecular solvents such as ethanol, toluene, DMF, or DMSO showed no conversion beyond 30% even after 24 h and in acetic acid gave 80% conversion only after 6 h of reflux, thus underscoring the role of the ionic liquid in efficiently promoting the reaction.[124]

Xia and Lu[125] also published the synthesis of 2,4,5-triarylimidazoles **31** using the ionic liquid [HeMIM][BF_4]. The method entailed the condensation reaction of **29** with **8** and **30** using microwave irradiation (Scheme 7). The results show that there were no remarkable differences in yields and reaction times between aromatic aldehydes **8** with electron-donating groups and those with electron-withdrawing groups. On the other hand, however, aliphatic aldehydes **8** with long chains such as heptaldehyde were unable to provide the desired product in an acceptable yield. The ionic liquid was used in a molar ratio of 1:12 (reactant/IL), and it was shown that the ionic liquid was an extremely suitable catalytically active medium. The ionic liquid was recovered, and the yields of the products remained the same even after the ionic liquid was reused three times. The traditional method for preparing imidazoles **31** is to reflux the mixture of diketones, bisaldehydes, and NH_4OAc in acetic acid for 5 h, which affords similar yields.[125]

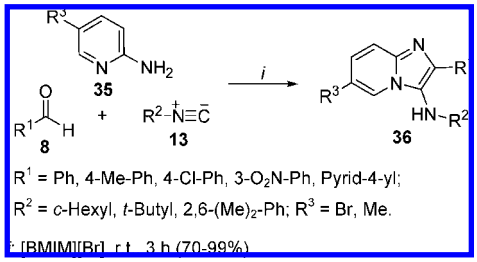
Scheme 8



Srinivasan et al.[126] reported a one-pot synthesis of 2-aryl benzimidazoles **34** initiated by imidazolium-based ionic liquids. The reaction occurred at room temperature without the need for a catalyst. The compounds were obtained in good yields (82−94%) by reacting 1,2-phenylenediamines **32** with benzoyl chlorides **33** for a short time (10−20 min), as shown in Scheme 8. It is important to mention that there have been previous reports of benzimidazoles **34** produced in a two-step procedure where **32** is treated with 1 equiv of **33** and the resulting monoacylated product is subjected to cyclodehydration under harsh conditions such as heating in aqueous acids and pyrolysis at temperatures between 200 and 350 °C.[126] Thus, in the reaction using ionic liquid, the authors believed it was most likely that the hydrogen bond interaction between the most acid hydrogen (NH or CH) of the imidazolium cation and the carbonyl oxygen during both the step of acylation and the step of cyclodehydration of the monoacylated product may have promoted the overall reaction. In this protocol, the ionic liquid was used in a molar ratio of 1:1 (reactant/IL), and the ionic liquid was recovered almost completely and recycled twice with only a marginal loss in yield the second time it was reused.

Another kind of imidazole derivative, imidazo[1,2-*a*]pyridine, also represents an important class of pharmaceutical compounds.[127] To date, several synthetic methods have been reported for the preparation of imidazo[1,2-*a*]pyridine ring systems: (i) a five-membered ring is constructed by condensation of 2-aminopyridines with α-haloketones or α-haloaldehydes; (ii) a six-membered ring is constructed from the annulation of imidazoles or the reaction of cyclic ketene aminals; (iii) both of these rings are formed.[81e,127–132] Several isocyanide-based MCRs have been reported for the synthesis of imidazo[1,2-*a*]pyridines by the condensation of an aldehyde, an isocyanide, and a 2-aminoazine in the presence of a strong protic acid[133–135] (AcOH, $HClO_4$) or Lewis acid ($Sc(OTf)_3$).[135] Shaabani et al.[81e] developed a synthesis for 3-aminoimidazo[1,2-*a*]pyridines **36** via a three-component condensation reaction of aldehydes **8**, 2-amino-5-methyl-[Br]pyridines **35**, and isocyanides **13** at room temperature in the presence of [BMIM][Br] (Scheme 9). The ionic liquid was used in a molar ratio of 1:1.4 (reactant/IL), and it was recycled and reused four times with a gradual decrease in the yield of **36** (95%, 92%, 90%, 85%). The reaction between **8**, **35**, and **13** was also studied in the absence of [BMIM][Br], and the yield of **36** was only 25% at room temperature after 12 h, demonstrating that [BMIM][Br] was indeed an

Scheme 9

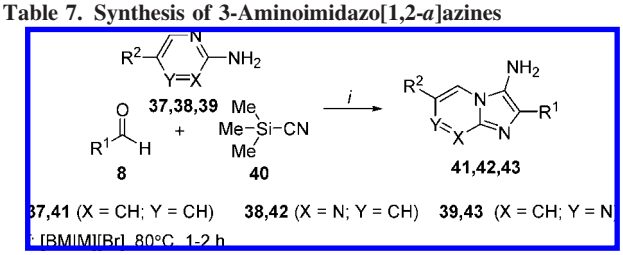


important component of the reaction.[81e] The solvophobic effects[136]of ILs are interesting due the increasing use of surfactants in applications that require water-free or water-poor media.[137] It has been suggested by some researchers that ILs can form aggregates.[138]In fact, micelle formation of selected ionic liquids in solution has already been found to take place.[139–144] The possibilities of micelle formation may have also consequences in the solvation properties of the IL molecules by simple solutes and the formation of dispersed or phase-separated systems. The solvophobic effects of ILs could be responsible for fast and easy approximation of solute (reactant) molecules in the reaction media. The authors believed that in this reaction, the solvophobic properties of ionic liquids are able to promote the association of the reactants in a solvent cavity during the activation process and thereby accelerate the reaction. This property of ionic liquids is especially efficient for MCRs, in which the entropy of the reaction is decreased in the transition state.[8,9,10,145] The same procedure performed in toluene under reflux and NH_4Cl took 30 h and afforded yields of only 49−65%,[146] clearly demonstrating the advantages of using ionic liquids.

In another study, Shaabani and Maleki[147] reported the synthesis of 3-aminoimidazo[1,2-*a*]azines **41**−**43**, using ionic liquids ([BMIM][Br]) as a promoter under classical heating conditions, as shown in Table 6. This synthesis proceeded through a multicomponent reaction involving the condensation of aldehydes **8**, 2-aminoazines **37**−**39**, and TMSCN **40**. The effect of using a variety of **8** and aminoazines **37**−**39** was examined for this reaction and in all cases the products were obtained efficiently, under mild conditions. The ionic liquid was used in a molar ratio of 1:1.4 (reactant/IL) and was recycled and reused four times (Table 7, entry 1; 90%, 86%, 85%, and 80% yields). To illustrate the benefit of using the ionic liquid for these reactions, an experiment was conducted in the absence of an ionic liquid. The yield in that case was only 5% after heating at 80 °C for 3 h. In molecular solvents, the reaction only proceeded with catalysts, such as $Sc(OTf)_2$, $HClO_4$, or AcOH, at room temperature for 48 h and yielded no more than 65%.[148]

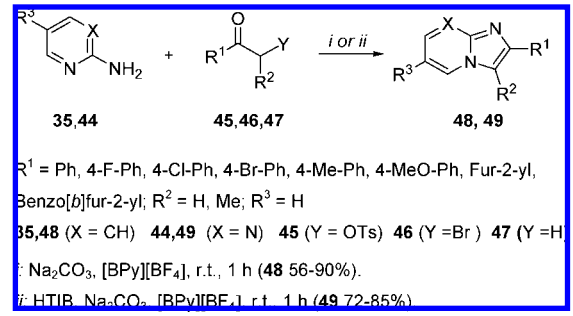
Imidazo[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines constitute an important class of organic compounds that have been widely used as azodyes,[149] fabric whitener,s[150] and antimicrobial agents. Despite their wide applicability, feasible routes to their synthesis are limited. Typically, they are synthesized by the cyclocondensation of 2-aminopyrimidine with a suitable α-bromoacetophenone in solvents such as DME,[151]ethanol,[152] acetone,[153] and DMF.[154] Unfortunately, a long reaction time is necessary and the yield is poor. Therefore, Xie[155] and Chen et al.[156] investigated the use of ionic liquids in the synthesis of imidazo[1,2-*a*] pyrimidines **49** and imidazo[1,2-*a*]pyridines **48** from the cyclocondensation of 2-aminopyrimidines **44** or 2-aminopyridines **35**, respectively, with a suitable α-bromoacetophenones **45**−**47**.

Table 7. Synthesis of 3-Aminoimidazo[1,2-*a*]azines



entry	R_1	R_2	X	Y	time (h)	yield (%)
1	4-Cl-Ph	Me	CH	CH	1.0	92
2	4-Me-Ph	Me	CH	CH	1.2	87
3	3-O_2N-Ph	Me	CH	CH	1.2	85
4	Ph	Me	CH	CH	1.5	77
5	4-pyridyl	Me	CH	CH	2.0	80
6	2-pyridyl	Me	CH	CH	2.0	62
7	Ph	Br	CH	CH	1.5	83
8	4-MeO-Ph	H	N	CH	2.0	60
9	4-O_2N-Ph	H	N	CH	2.0	75
10	4-MeO-Ph	H	CH	N	1.5	72
11	4-O_2N-Ph	H	CH	N	1.5	84

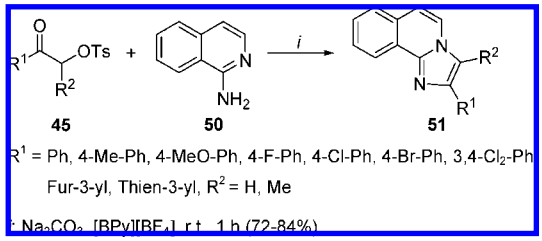
Scheme 10



Xie[155] found that α-tosyloxylation (bromination) of ketones can be performed by treating the ketones with HTIB and 2-aminopyrimidine successively in $[Bpy][BF_4]$. As a consequence of this finding, the author reasoned that imidazo[1,2-*a*]pyrimidine **48** and **49** could be directly prepared by a one-pot procedure[155] (Scheme 10). In all of these cases, the ionic liquid was used in a molar ratio of 1:10 (reactant/IL), and it was reused four times with a gradual loss of activity (90%, 86%, 85%, and 80% yields). The reaction performed in ILs showed a rate acceleration and increase of yield compared with the rection performed in molecular solvents, such as acetonitrile, where the preparation of imidazo[1,2-*a*]pyridines **48** required refluxing for 6−24 hours and the yield was only 37%.[157–162] For preparation of 2-phenylimidazo[1,2-*a*]pyrimidines **49** refluxing for 6 h in a molecular solvent such as ethanol was necessary.[155]

The methods used for the synthesis of imidazo[2,1-*a*]isoquinoline include the cyclization of phenacylisoquinolinium bromide with ammonium acetate in acetic acid,[163] the reaction of α-bromoacetophenone phenylsulfonylhydrazones with isoquinoline,[164] the 1,5-dipolar cyclization reaction of isoquinolinium *N*-ylides using *N*-bis(methylthio)methylene-*p*-toluenesulfonamide[165] and the condensation of 1-amino-2-(α-benzotriazol-1-yl methyl) isoquinolinium chloride with aryl aldehydes.[159] There is one report on the synthesis of imidazo[2,1-*a*]isoquinolines using an ionic liquid. Chen et al.[166] reported the use of ionic liquids as solvent in a molar ratio of 1:10 (reactant/IL) in the cyclocondensation reaction of α-tosyloxyketones **45** with 1-amino isoquinoline **50** in $[BPy][BF_4]$ at room temperature and in the presence of sodium carbonate (Scheme 11). The mixture

Scheme 11



was stirred for about 1 h and gave the desired imidazo[2,1-*a*]isoquinolines **51** in good yields. The ionic liquid was recycled and reused three times with no appreciable decrease in yield (81%, 82%, and 80%) of **51**. When the reaction was conducted in classical molecular solvents, such as acetonitrile, the preparation of 2-phenylimidazo[2,1-*a*]isoquinoline **51** required refluxing for 5 h.[166]

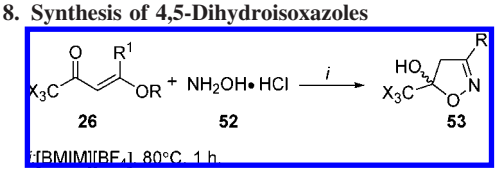
5.6. Isoxazoles

Isoxazoles and their derivatives have been recognized as highly useful in medicinal chemistry. In particular, many trihalomethylated azoles are known to exhibit important biological activities in the fields of both medicine and agriculture.[106a–d,167–169] Among the methods available for the preparation of substituted isoxazoles, the oximation of 1,3-dicarbonyl compounds (mainly β-ketoaldehydes and β-diketones) and the cyclocondensation of nitrile oxides to unsaturated compounds are by far the most widely utilized.[170] As previously mentioned, in the course of extensive investigations on the synthesis of heterocycles, Martins et al.[108] have developed a general procedure for the synthesis of a large number of 1,1,1-trihalo-4-alcoxy-3-alken-2-ones,[108a,b] important halogen-containing building blocks, and demonstrated their usefulness in heterocyclic preparations.[108c] Since 1991, the scope of this reaction has been expanded by these authors with the publication of a series of papers on the synthesis of 5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles using conventional methods, in which the general procedure involves the reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with a saturated aqueous solution of hydroxylamine hydrochloride in a mixture of water and pyridine at 35−70 °C, with reaction times ranging between 8 and 16 h.[108,171,172] Thus, considering the importance of this class of compounds, we reported here for the first time the ionic liquid promoted synthesis of trihalomethyl-substituted 4,5-dihydroisoxazoles **53**[108e] (Table 8). 4,5-Dihydroisoxazoles **53** were obtained from the cyclocondensation reaction of enones **26** with hydroxylamine hydrochloride **52** at 80 °C for 1 h (Table 8). The ionic liquid was used in a ratio of 1:1 (reactant/IL), and the advantages observed in this reaction were the same as those observed in the synthesis of 4,5-dihydropyrazoles **28**.

5.7. Oxazoles, Oxazolines, and Oxazolidinones

Oxazoles are key building blocks or synthetic intermediates for pharmaceutical products.[173] They are most commonly obtained by the Hantzsch reaction[174] or the cyclodehydration of β-ketoamides.[175] The dehydrogenation of oxazolines[176] and other processes such as aza-Wittig reactions,[177]Schmidt rearrangements,[178] the use of isocyanides,[179] TosMIC,[180] and intramolecular alkyne additions[181] have also been employed. An interesting conversion of ketoximes to oximes via *N*,*N*-diacylated enamides was reported in 1980 by Bhat and Reddy.[182] Although oxazoles

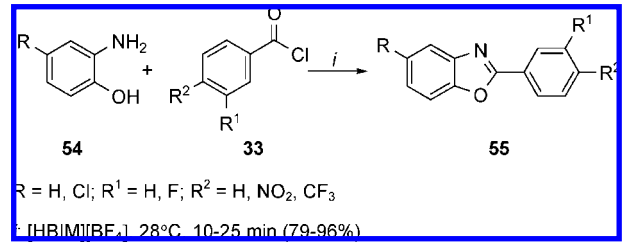
Table 8. Synthesis of 4,5-Dihydroisoxazoles



entry	R	R^1	X	yields (%) conventional method[a]	yields (%) [the present study][b]
1	Et	H	Cl	78	78
2	Me	Me	Cl	82	84
3	Me	Ph	Cl	90[c]	89
4	Et	H	F	68	80
5	Me	Me	F	70	85
6	Me	Ph	F		90

[a] H_2O, 40 °C, 16 h.[108a] [b] IL was used in a ratio 1:1 (reactant/IL). [c] MeOH, reflux, 16 h.[172]

Scheme 12



possess widespread applications in diverse areas, there are few papers that highlight the improvement of synthetic methods to obtain these heterocycles. However, Srinivasan et al.[126] described the utilization of ionic liquids as reaction media to obtain 2-phenyl benzoxazoles **55** from 2-aminophenols **54** and benzoyl chlorides **33** at room temperature (Scheme 12). The rationale for the efficacy of ionic liquids to promote these heterocyclizations was considered the same as that mentioned by the author for the synthesis of benzimidazoles **34**.[126] In both procedures, the ionic liquid was used in a molar ratio of 1:1.5 (reactant/IL) and was recovered almost completely and recycled twice with only a marginal loss in yield on the second time it was reused.

2-Oxazolines are an important class of heterocycles that have held the fascination of many synthetic chemists.[183] 2-Oxazolines have been used as chiral auxiliaries, ligands for metal entrapment, and, of particular importance, as a protecting group for carboxylic acids and amino alcohols.[184] Methods to synthesize 2-oxazolines have been extensively explored. The most commonly used methods are (i) the reaction of amino alcohols with carboxylic acids[185] or carboxylic acid derivatives (ortho-esters, nitriles, imino ether hydrochlorides, and acyl benzotriazoles)[186] and (ii) the cyclodehydration of β-hydroxyamides with a number of reagents including the Burgess reagent, DAST, PPh_3/DEAD, and the Vilsmeier reagent.[176a,187]

A synthetic approach to obtain oxazolines **58** using ionic liquids was described by Kamakshi et al.[188] This method combined amide bond formation from acids **56** and amino alcohols **57** and cyclic dehydration in a one-pot synthesis. The protocol afforded good yields of substituted 2-oxazolines **58** in indium chloride/ionic liquid media ([BMIM][Cl]), as shown in Scheme 13. The ionic liquid was used in a molar ratio of 1:7 (reactant/IL). The authors conjectured that the higher reactivity of the carboxylic acids with electron-withdrawing groups could be explained by the electrophilicity

Scheme 13

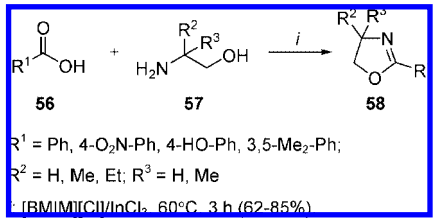
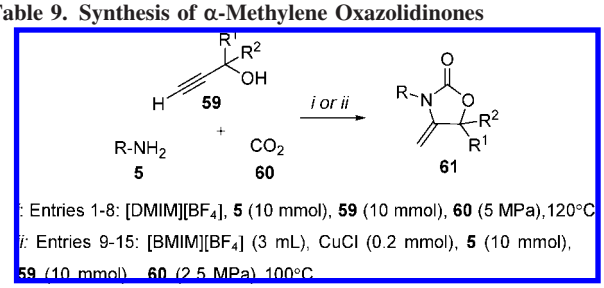


Table 9. Synthesis of α-Methylene Oxazolidinones



			without CuCl		with CuCl	
entry	R^1/R^2	R	time (h)	yield (%)	time (h)	yield (%)
1	Me/Et	*c*-hexyl	10	52.9	10	
2	Me/*i*-Pr	*c*-hexyl	10	51.3	15	84
3	$-(CH_2)_5-$	*c*-hexyl	10	87.3	10	81
4	Me/Ph	*c*-hexyl	10	88.6	15	95
5	Me/H	*c*-hexyl	10		15	
6	H/H	*c*-hexyl	10		15	
7	Me/Me	*c*-hexyl	10	83.3		
8	$-(CH_2)_4$	*c*-hexyl	10		12	87
9	$-(CH_2)_5-$	$PhCH_2$			10	88
10	$-(CH_2)_5-$	allyl			10	78
11	$-(CH_2)_5-$	Bu			10	80
12	$-(CH_2)_5-$	pentyl			10	89
13	$-(CH_2)_5-$	Ph			10	0
14	$-(CH_2)_5-$	$H_2N-(CH_2)_6-$			10	82

of the carbonyl carbon being enhanced by the presence of electron-withdrawing groups in the phenyl ring. The reverse occurred for donating substituents, which could have hindered the attack in step 2 in which there is elimination of a water molecule. When the reaction was performed without the presence of an ionic liquid, in chlorobenzene under reflux conditions (3 h) with $InCl_3$ as a catalyst, the product yield was only 50%.[188]

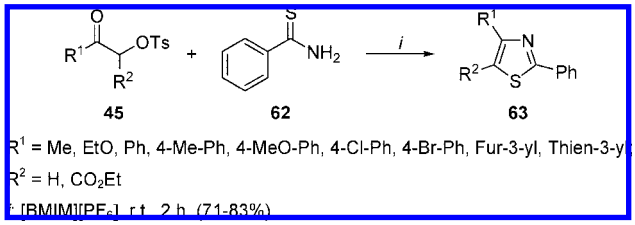
Oxazolidinones are important heterocyclic compounds showing a wide range of applications, including as intermediates[189] and chiral auxiliaries[190] in organic synthesis and as antibacterial drugs in pharmaceutical chemistry.[191] The three main strategies used for the preparation of oxazolidinones are (i) the reaction of amino alcohols with phosgene,[192] urea,[193] or dialkyl carbonates,[194] (ii) the insertion of carbon dioxide in the aziridine moiety,[195] and (iii) the reaction of propargylamines (or propargylic alcohols and amines) with carbon dioxide.[196] Ionic liquids have been found to be efficient catalysts and reaction media for the activation of CO_2,[197] and this method was adapted by Deng et al.[197a] for the one-step synthesis of N-substituted 4-methylene-2-oxazolidinones **61** in the presence of propargylic alcohols **59** (Table 9).[197a] The reaction between cyclohexylamine and 2-methyl-3-butyn-2-ol hardly occurred if dimethyl sulfoxide and toluene were used as solvents and 44.1−91.6% yields could be obtained in the presence of ionic liquids. For ionic liquids containing a [BMIM] cation, the best results were achieved in the presence of [BMIM][BF_4] (81% yield). The application of an ionic liquid with the [PF_6] anion gave a relatively poor result (44% yield), which could be related to the instability of the PF_6 anion under the reaction conditions. The catalytic activity was gradually improved with increasing number of carbons in the alkyl chain, and 91.6% yield was achieved when ionic liquid [DMIM][BF_4] was used. Cyclohexylamine was chosen because the authors found that aliphatic amines allowed better results than aromatic amines, which have weak nucleophilic ability. The activity of ionic liquid ([DMIM][BF_4]) in the reaction of cyclohexylamine with different propargylic alcohols was investigated. The results are summarized in Table 9 (entries 1−6). In this procedure, the ionic liquid was used in a molar ratio of 1:1.5 (reactant/IL), and it was recovered and reused twice with no appreciable decrease in yield (83.3−77.5%). The same reaction process was performed in the presence of CuCl in catalytic quantities.[197b] In presence of CuCl, the reaction of 1-ethynyl-1-cyclohexanol with several amines (Table 9, entries 2, 3, 4, 7−12, and 14) show similar results to the cyclohexylamine. CuCl was capable of catalyzing the synthesis of α-methylene oxazolidinones **61**, but the efficiency appears to be only slightly superior compared with the same reaction without a catalyst (Table 9). The ionic liquid was used in a ratio of 1:1.5 (reactant/IL), and [BMIM]BF_4/CuCl was recovered and reused four times with no appreciable decrease in yield. The synthesis of N-substituted 4-methylene-2-oxazolidinones **61** from aliphatic amines **5** and 2-methyl-3-butyn-2-ol **59** gave extremely poor yields (3−4%) when DMSO and toluene were used as solvent, whereas 44−91% yields were obtained in the presence of the ionic liquids.

5.8. Thiazoles and Thiazolidinones

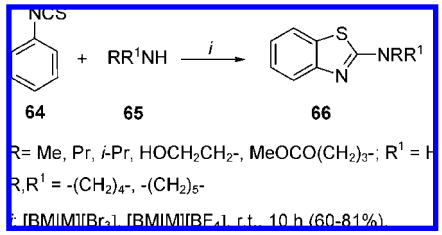
Many thiazoles have emerged as active pharmaceutical ingredients in several drugs due to their potential anti-inflammatory,[198] antitumor,[199] antihyperlipidemic,[200] and antihypertensive[201] properties, among several other biological properties.[202] Several methods[203] for the synthesis of thiazoles have been developed by Hantzsch, Tcherniac, Cook-Heilbron, Gabriel, and several other groups, among which the most widely used method is Hantzsch's synthesis[203,204] (the reaction between α-halocarbonylic compounds and thioamides, thioureas, or thiocarbamic or dithiocarbamic acids). Relatively newer methods include the cycloaddition of TosMIC to thione derivatives,[205] the oxidation of thiazoline or thiazolidine ring systems,[206] and Ugi reactions,[207] among others.[208] Despite these procedures, novel methods for thiazole synthesis are still in demand. In order to meet this need, some researchers have been developing methodologies using ionic liquids to synthesize these heterocycles. Chen et al.[209] published a method to synthesize substituted 2-thiazoles **63** using ionic liquids. The reaction was carried out through the cyclocondensation of α-tosyloxyketones **45** with thiobenzamide **62** in [BMIM][PF_6] at room temperature for about 2 h (Scheme 14). In this method, ionic liquid was used in a molar ratio of 1:10 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in the yield of **63** (78%, 77%, and 79%). On the other hand, when this reaction was carried out with the classical molecular solvent dichloromethane, the preparation of 2,4-diphenylthiazoles **63** required refluxing for 7 h.[209]

Le et al.[210] introduced an efficient method to produce substituted 2-benzothiazoles **66** via a one-pot reaction using

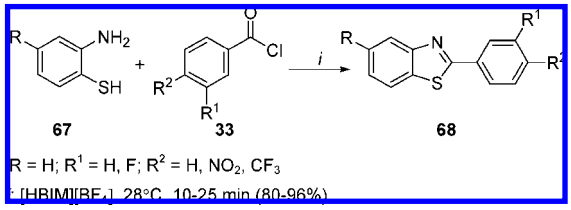
Scheme 14



Scheme 15



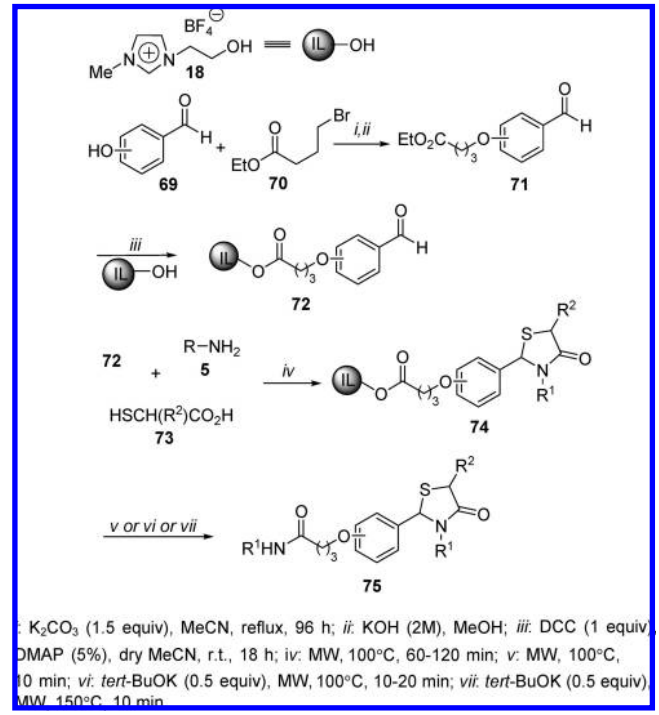
Scheme 16



[BMIM][Br_3] as a new reactant, and [BMIM][BF_4] was used in a molar ratio of 1:5 (reactant/IL). The reaction was carried out starting from phenyl isothiocyanate **64** and amines **65** (Scheme 15). The authors maintained that this method had many obvious advantages compared with those reported in the literature, including high yields and shorter reaction times. For example, the synthesis of 2-(propylamino)benzothiazole, 2-(*N*-piperidino)benzothiazole, and pyrrolidinobenzothiazole required overnight reactions, and the yields were only 73%, 69%, and 7%, respectively.[210]

Srinivasan et al.[126] also reported a regioselective one-pot synthesis of substituted 2-benzothiazoles **68** promoted by imidazolium-based ionic liquids. The reaction was performed at room temperature without the need for a catalyst. The 2-aryl benzothiazoles **68** were obtained in good yields by the reaction of 2-aminothiophenols **67** with benzoyl chlorides **33**, in a short reaction time (Scheme 16). Two ionic liquids were used, [HBIM][BF_4] and [BBIM][BF_4], and the former proved much faster than the latter. This may have been due to the higher Brønsted acidity conferred by the −NH proton of [HBIM][BF_4] compared with the more acidic C2−H proton of [BBIM][BF_4]. The ionic liquid was used in a molar ratio of 1:1 (reactant/IL), and it was recovered almost completely and recycled twice with only a marginal loss in yield the second time it was recycled. It is important to mention that similar to 1,2-phenylenediamines **32**(Scheme 8) and 2-aminophenols **54** (Scheme 12), 2-aminothiophenols **67** treated with an equivalent of benzoyl chloride **33** followed by dehydration under harsh conditions resulted in thiazole **68**. The authors believed that, in all probability, the hydrogen bond interaction of the most acidic hydrogen (NH or CH) of the imidazolium cations of the ionic liquids with the carbonyl oxygen both during the step of acylation and during the step of cyclodehydration of the monoacylated product may have promoted the overall reaction.[126]

Table 10. Synthesis of 4-Thiazolidinones

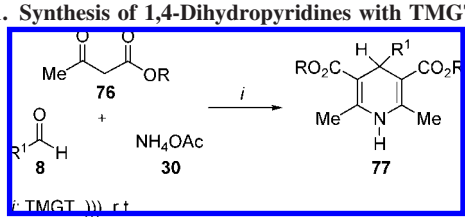


entry[a]	R^1	R^2	time[b] (min)	yield (%)[c]
1	Bn	H	90	86
2	Bn	Me	90	79
3	Bn	CH_2CO_2H	90	60
4	piperonyl	H	120	71
5	$CH_2CH(OMe)_2$	H	120	84
6	CH_2−CH=CH_2	H	120	82
7	Pr	H	80	41
8	*i*-Pr	H	60	12
9	*i*-Bu	H	120	42
10	Bn	H	120	61
11	Pr	H	120	71
12	*i*-Bu	H	120	47

[a] Data refers to step iv. [b] Reactions were run in a focused microwave reactor at 100 °C, MW = 60 W. [c] Conversion estimated from the crude reaction mixture by ^{1}H NMR.

4-Thiazolidinones have been reported to possess a wide range of biological activities, including antifungal,[211] antimicrobial,[212] and inflammatory activity.[213] These heterocycles are most conveniently synthesized by a three-component condensation of a primary amine, an aldehyde, and a mercaptoacetic acid. Usually, the reaction proceeds through the intermediate imine, but the stepwise assembly of 4-thiazolidinones has also been reported.[214] There have been reports describing the solid phase synthesis of 4-thiazolidinones[215] and a few reports[216]where the nitrogen of this heterocycle originated from an α-amino acid with the carboxylic function serving as the site of attachment to the support. In a previous paper, Bazureau and Fraga-Dubreuil[217] found that a functionalized PEG-ILPs could be used as a novel matrix in a liquid organic phase. The authors confirmed the versatility of the functionalized ionic liquid phase in obtaining 4-thiazolidinones **75** (Table 10). Ionic liquid **18** contains the alcohol function responsible for the reaction support. The conventional procedure for thiazolidinone by this synthetic route is carried out by using toluene and heating at 130 °C for 16 h, and the yields are between 63% and 89%.[218] Thus, the utilization of a functionalized ionic liquid

Table 11. Synthesis of 1,4-Dihydropyridines with TMGT



			yield, % (time, h)	
entry	R^1	R	I[a]	II[b]
1	Ph	Et	90 (2); 30(3)[c]	87 (7)
2	4-MeO-Ph	Et	88 (2); 27 (3)[c]	74 (6.5)
3	3-MeO-Ph	Et	82 (5); 84 (2.3)[d]	79 (8)
4	4-Me-Ph	Et	84 (2.3)	84 (8.3)
5	2-MeO-Ph	Et	95 (2.15)	78 (6)
6	3-Cl-Ph	Et	90 (1.45)	80 (6.5)
7	3-O_2N-Ph	Et	94 (2)	85 (7)
8	4-O_2N-Ph	Et	22 (3)[c]	84 (8.5)
9	4-Br-Ph	Me	86 (2.15)	83 (8)
10	4-O_2N-Ph	Me	87 (1.45)	87 (7.50)

[a] In the presence of TMGT and using ultrasound irradiation. [b] In the presence of TMGT without using ultrasound irradiation. [c] In the absence of TMGT without using ultrasound irradiation. [d] The same TMGT was used for each of the four runs.

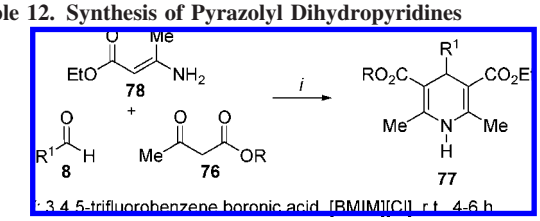
as a novel matrix in a liquid organic phase showed advantages in comparison with the same reaction performed in molecular solvents. The possibility of employing a functionalized IL in microwave synthesis makes the reaction faster than that carried out in molecular solvents.

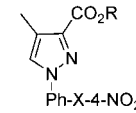
6. Synthesis of Six-Membered Heterocycles

6.1. Pyridines

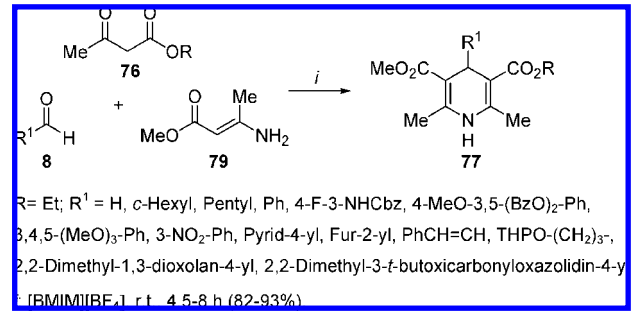
It is well known that 1,4-dihydropyridines exhibit a wide range of biological activities.[219,220] The 1,4-dihydropyridines are generally synthesized by the Hantzch method.[221] The original Hantzsch dihydropyridine synthesis consisted of the cyclocondensation reaction of ethyl acetoacetate (2 equiv) with an aldehyde and ammonia[221] either in acetic acid or by refluxing in alcohols for long periods, leading, in general, to low yields.[222,223] Shaabani et al.[224] introduced ionic liquids and presented a modified method of the original Hantzsch dihydropyridines **77** synthesis. The synthesis was performed from a three-component condensation in combination with TMGT as the ionic liquid, using ultrasound irradiation at room temperature (Table 11). Dihydropyridines **77** were obtained from the reaction between aldehydes **8**, β-ketoesters **76**, and ammonium acetate **30** in a catalytic amount of ionic liquid in a molar ratio of 1:0.5 (reactant/IL), which was recovered and reused four times with no appreciable decrease in yield (entry 1, 88%, 88%, 87%, and 84% yields). When TMGT was used as the promoter for the Hantzsch 1,4-dihydropyridines **77** synthesis, not only was there a dramatic improvement in yields (84−95%) at room temperature compared with conventional thermal heating, but there was also a considerable decrease in the reaction times (1−2 h) compared with the classical synthesis (6−8 h). Ultrasound irradiation was essential in obtaining the high conversions of this condensation, because without it there was close to a 4-fold increase in the reaction time. The scope of the reaction was then extended to β-ketoesters **76** with various aromatic aldehydes **8** carrying either electron-releasing or electron-withdrawing substituents at the 4-position. It was found that the reactions proceeded very efficiently in all cases and that the reaction times decreased for electron-withdrawing substituents.

Table 12. Synthesis of Pyrazolyl Dihydropyridines



Entry	R^1	X	R	Yield (%)
1		H	Me	92
2		H	Et	86
3		H	Me	87
4		H	Et	91
5		NO_2	Et	85
6		H	Et	87
7	Ph	-	Et	90
8	3-NO_2-Ph	-	Et	93

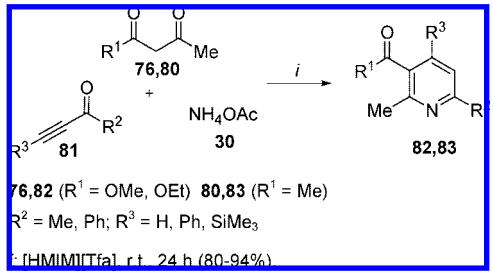
Scheme 17



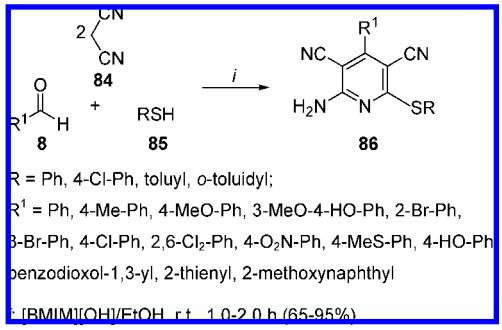
Perumal and Sridhar[225] also reported the use of ionic liquids as reactional media to synthesize dihydropyridines **77**. The reaction consisted of another modification of the original Hantzsch dihydropyridine synthesis, where aldehydes **8** reacted with enaminoesters **78** and β-ketoester **76**. Enaminoesters **78** served as a source of ammonia leading to a series of 1,4-dihydropyridines **77** of interest[226] (Table 12). The use of [BMIM][Cl] in a molar ratio of 1:5 (reactant/IL) at room temperature afforded the products in high yields and a short reaction time. The ionic liquid was recovered and reused twice with no appreciable decrease in yield. Furthermore, the addition of 5 mol % of 3,4,5-trifluorobenzene boronic acid to the reaction mixture ensured excellent yields of the product. When compared with other catalysts, it is clear that 3,4,5-trifluorobenzene boronic acid was superior for the [BMIM][Cl] mediated synthesis.[225] The authors considered that the increase in yield might have been due to the increase in the acidity of the reaction mixture. The use of the ionic liquid increased the reaction performance considering that the reaction carried out in molecular solvents under reflux, for example, in ethanol (8 h), gave poor yields (48%).

The versatility of ionic liquids in the synthesis of 1,4-dihydropyridines was also explored by Yadav et al.[227]The reaction was performed using enaminoesters **79** as a source of ammonia at room temperature. The condensation reaction of benzaldehydes **8** and ethyl acetoacetates **76** with **79** in [BMIM][BF_4] afforded the corresponding 1,4-dihydropyridines **77** in 80−90% yields (Scheme 17). The ionic liquid was used in a molar ratio of 1:5 (reactant/IL), and it was recovered and reused twice with similar yields. In the fourth reuse, the yields were slightly decreased. This method was

Scheme 18



Scheme 19

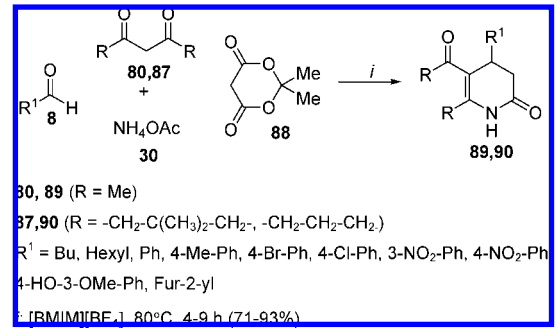


compatible with highly acid-sensitive protecting groups such as THP ethers, acetals, aminoacetals, and carbamates present in the substrate. In addition, it was equally effective for both electron-rich and electron-deficient aldehydes **8**. Once again, the improvement in the reaction caused by the presence of ionic liquid was evident; taking into account the fact that the products were obtained in low to moderate yields (55−67%) after a long reaction period (15−24 h) when the reaction was carried out by refluxing in ethanol.[227]

Perumal and Karthikeyan[228] designed a methodology using ionic liquid for the synthesis of pyridines **82** and **83** by generating the enaminone from the corresponding β-ketoesters **76** and **80** for an *in situ* heteroannulation in the Bohlmann−Rahtz reaction. The one-pot, three-component reaction of 1,3-dicarbonyl compounds **76** and **80**, ammonium acetate **30**, and alkynones **81** in [HMIM][Tfa] as solvent gave good results (Scheme 18). 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).[229]

Ranu et al.[230] reported the use of [BMIM][OH] in a protocol to synthesize polyfunctionalized pyridines. The conventional method for this reaction involves the condensation of aldehydes **8**, malononitrile **84**, and thiols **85** to afford highly substituted pyridines **86** (Scheme 19). 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 bases such as DABCO and Et_3N are used in ethanol under reflux (2−3 h).[231] Ranu et al.[232] discovered 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 19). A wide range of substituted aromatic and heteroaromatic aldehydes **8**, as well as several substituted thiophenols **81**, underwent this three-component condensation with malononitrile. The ionic liquid was used in a molar ratio of 1:0.5 (reactant/IL), and the authors claimed that the presence of the ionic liquid, [BMIM][OH], was essential, being that in its absence the reactions did not proceed at all. 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.

Scheme 20



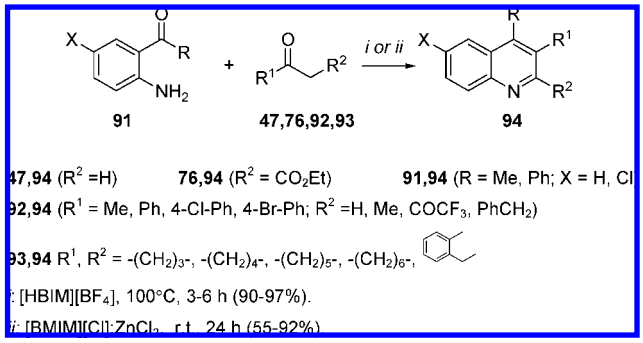
Zhang et al.[233] innovated the use of ionic liquids as reaction media for the synthesis of 1,4-dihydropyridines **89** and **90**. The protocol consisted of a four-component reaction utilizing aldehydes **8**, 1,3-diketones **80** and **87**, Meldrum's acid **88** and ammonium acetate **30** (Scheme 20). The investigations showed that not only aromatic aldehydes **8** but also heterocyclic and aliphatic aldehydes **8**, underwent the reaction effectively to afford the corresponding products in good yields.[233] The ionic liquid was used in a molar ratio of 1:2.5 (reactant/IL), and it was recovered and reused four times with almost no decrease in efficiency. Similar to the three-component reaction demonstrated by Yadav et al.,[227] when this reaction was carried out in ethanol under reflux, the products were only obtained after a long reaction period (15−24 h). This finding supports the fact that ionic liquid plays an important role in improving the synthesis of 1,4-dihydropyridines from condensation reactions.

6.2. Quinolines

The quinoline nucleus is found in several natural compounds and pharmacologically active substances and displays a broad range of biological activity.[234] The best-known method for obtaining quinolines and related polyheterocycles is the Friedlander quinoline synthesis.[235] The Friedlander synthesis can be catalyzed by strong acids or bases or may take place without a catalyst at higher temperatures. However, both the harsh reaction conditions necessary and the need for a strong acid or base catalyst, which is incompatible with either acid- or base-sensitive groups, reduce the synthetic scope of this reaction. Recently, the Friedlander synthesis was reported in two other methods. In one of these, a novel traceless solid-phase was used,[236] and in the other, $NaAuCl_4$ was used as catalyst.[237] In this scenario, the use of ionic liquids has recently gained considerable importance. Srinivasan et al.[238] reported the use of ionic liquids in a molar ratio of 1:1 (reactant/IL) for the preparation of quinolines **94** using the Friedlander heteroannulation protocol, which made another catalyst unnecessary. 2-Aminoacetophenones **91** were reacted with a variety of ketones or ketoesters (**47**, **76**, **92**, or **93**) in ionic liquid as shown in Scheme 21.

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

Scheme 21

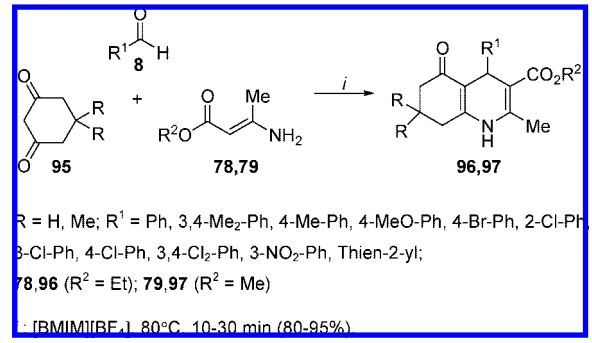


governed the electrophilicity of the imidazolium cation, which in turn had a bearing on the acidity of the ionic liquid. It was observed that the higher the basicity of the anion (increasing pK_a of the corresponding acid) the greater the increase in yield. [HBIM][BF_4] afforded the best result, and 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. The same reaction was investigated by Perumal and Karthikeyan[239] 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 **91** and ketones or ketoesters **47**, **76**, **92**, or **93** were mixed in the [BMIM][Cl]/$ZnCl_2$ melt and stirred at room temperature for 24 h to give quinolines **94** in good to excellent yields (Scheme 21). The ionic liquid was recovered and reused twice with no appreciable decrease in the yield of **94** (89%, 86%). Theoretically, the Friedlander 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. The reaction path suggested for the Friedlander synthesis involved a sequential formation of the *N*-(2-acylphenyl)-β-enaminone and cyclodehydration reaction.[239] The ionic liquid, promoting the Friedlander reaction with unsymmetrical ketones, regiospecifically afforded the 2,3-dialkylquinolines **94** in excellent isolated yields. The author mentioned that polarity and the large electrochemical window of the ionic liquid may have also contributed to the observed regiospecificity.[238] In the case of 2-aminoacetophenones **91**, the corresponding quinolines **94** were synthesized in excellent yields that were in fact superior to those reported from conventional procedures[237,240] using molecular solvent such as ethanol in reflux for 12 h.[241]

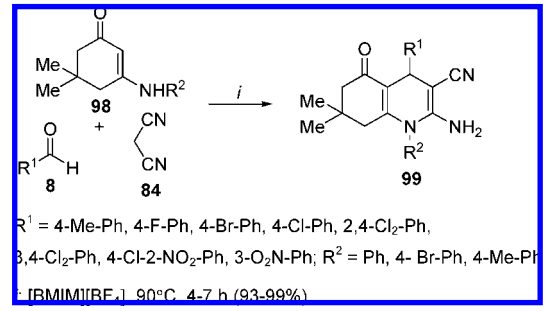
The use of an ionic liquid for the synthesis of hexahydroquinolones was studied by Wang et al.[242] 4-Aryl-5-oxo-1,2,3,4,5,6-hexahydroquinoline-3-carboxylates **96** and **97** were synthesized by the reaction of aromatic aldehydes **8**, 1,3-cyclohexanediones **95**, and enaminoesters **78** and **79** in [BMIM][BF_4] (Scheme 22). The ionic liquid was used in a molar ratio of 1:1 (reactant/IL) and was recovered and reused twice with no appreciable decrease in yield. Once again, in a fashion similar to that observed for the three-component reaction shown by Yadav et al.,[227] when the reaction was carried out in a molecular solvent such as ethanol,[227] a long reaction period (15−24 h) of reflux was necessary. In this case, the presence of ionic liquid dramatically reduced the reaction time.

Wang et al.[243] also published the synthesis of quinolines **99** using ionic liquids as solvent in three-component reactions with arylaldehydes **8**, cyclic β-enaminones **98** and different

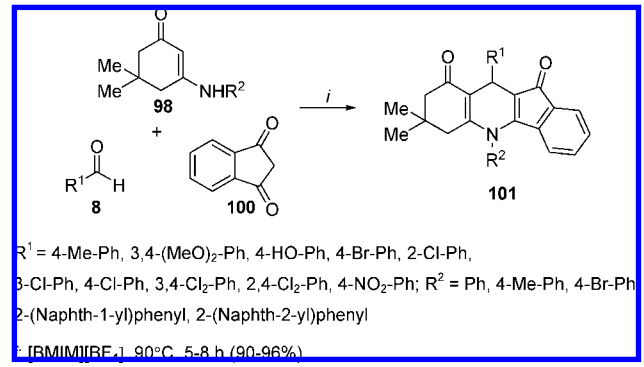
Scheme 22



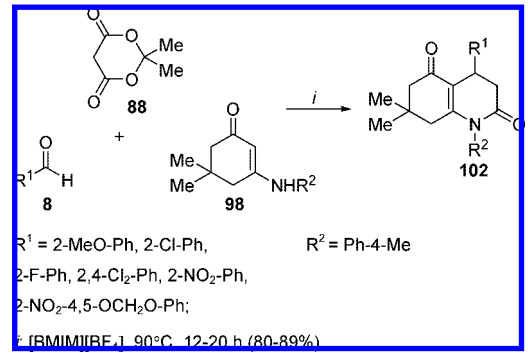
Scheme 23



Scheme 24

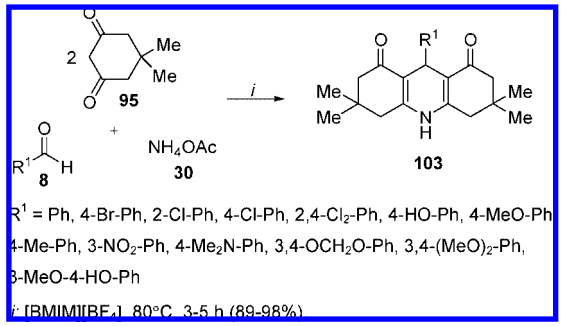


Scheme 25



active methylene compounds (Schemes 23–25). The ionic liquid was used in a molar ratio of 1:52 (reactant/IL), and the study began with malononitrile **84**. The results are summarized in Scheme 23. As expected, when the methylene compound **84** was replaced by 1,3-indenedione **100**, another series of quinolines **101** was obtained under the same reaction conditions. As shown in Schemes 23 and 24for the series of aldehydes **8**, the aromatic ring containing either electron-withdrawing groups (such as halide or nitro) or electron-donating groups (such as the alkyl group) reacted well with

Scheme 26



84 and **100** to give the corresponding products **99** and **101**, respectively, in high yields under the same reaction conditions. Therefore, it was concluded that there was no apparent effect produced from the electronic nature of the aromatic ring substituents in these reactions. When Meldrum's acid **88** was selected as the active methylene compound (Scheme 25), it was interesting that the desired products (obtained in Schemes 22 and 23) were not acquired at all, whereas tetrahydroquinolines **102** were obtained in good yields via an unexpected ring opening of the Meldrum's acid **88** reaction. Once more, compared with the same procedure using molecular solvents in methanol (11 h), acetonitrile (10 h), or ethanol (8 h) under reflux, this new method using an ionic liquid as solvent showed similar yields and the advantage of being environmentally benign.

6.3. Acridines

Acridines are well-known compounds because of their pharmacological profile as calcium channel modulators.[244] There are many methods for their synthesis carried out from aldehydes, dimedone, and ammonium acetate under a number of conditions, including by traditional heating in molecular solvents,[245] by using TEBAC in water as a catalyst,[246] or by using microwave irradiation.[247] Zong et al.[248] described the synthesis of tricyclic compounds, 9-arylpolyhydroacridines **103**, in an ionic liquid medium. When the three components, aromatic aldehydes **8**, 5,5-dimethyl-1,3-cyclohexanedione **95**, and ammonium acetate **30**, were treated in an ionic liquid [BMIM][BF_4] at 80 °C for a few hours, the desired 3,3,6,6-tetramethyl-9-aryl-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-diones **103** were obtained in high yields (89−98%) (Scheme 26). The ionic liquid was used in a molar ratio of 1:26 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in yield. The efficiency and scope of this procedure was demonstrated by the application of ionic liquids to the reaction of a variety of **8** with dimedone **95** in the presence of an excess of ammonium acetate **30**. Acridines **103** shown in this scheme were also synthesized by following the classical Hantzsch's procedure, which employs a reflux in molecular solvents such as ethanol for 1−2 h, however, the products were obtained in lower yields (50−70%).[249]

6.4. Pyrans

Polyfunctionalized 4*H*-pyrans are a privileged heterocyclic ring system because many of their derivatives possess useful pharmacological activities.[250] In addition, due to the inherent reactivity of the pyran ring, they are versatile building blocks.[251] 2-Amino-4*H*-pyrans have been routinely prepared from arylidenemalonitriles and activated methylene compounds in the presence of organic bases.[252] Many works describing the application of ionic liquids in reactions that produce pyrans can be found in the literature. Among them, Song et al.[253] reported the synthesis of 2-amino-4*H*-pyrans **104** and **105** from malononitrile **84**, aryl aldehydes **8**, and 1,3-dicarbonyl compounds **76** and **80**, using ionic liquids as soluble support. In this study, the reaction was performed using TMG−[BMIM][BF_4] in a molar ratio of 1:3 (reactant/IL), and it was recovered and reused five times with no appreciable decrease in yield as shown in Scheme 27. The electronic effects of phenyl ring substituents were also investigated, and it was shown that electron-donating groups disfavored product formation while electron-withdrawing groups favored their formation. In addition, it was found that ionic liquids were superior to ethanol (yields 60−80%) as solvent, in view of the higher isolated yields and reaction rates.

Song et al.[254] also published the synthesis of pyrans **104** using functionalized ionic liquid **18** under microwave irradiation (Table 13). A number of methods have been reported for the synthesis of pyrans in the presence of organic bases such as pyperidine in molecular solvents (e.g., ethanol

Scheme 27

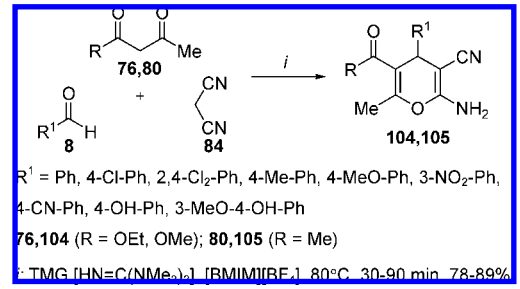
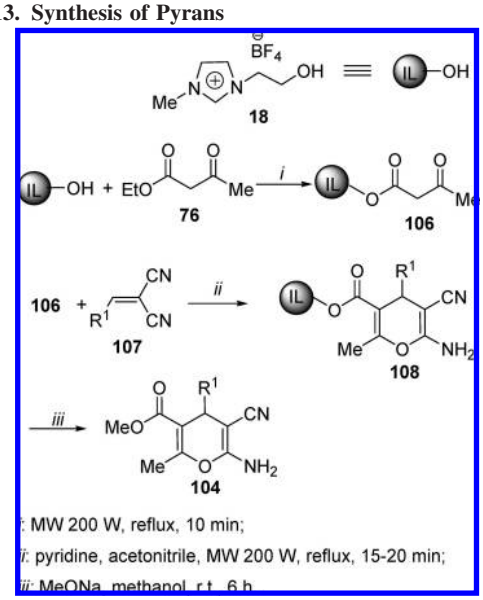


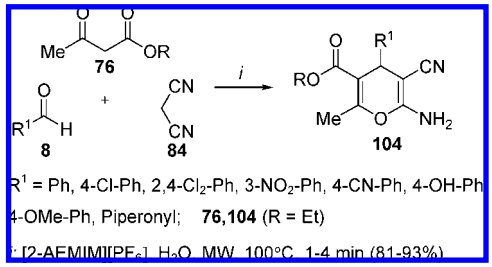
Table 13. Synthesis of Pyrans



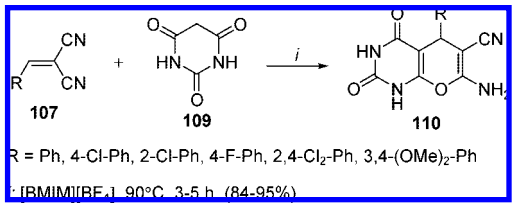
entry	R^1	time (min)[a]	yield (%)	final yield (%)
1	Ph	20	95	88
2	4-OH-Ph	20	93	84
3	4-OMe-Ph	20	94	86
4	4-Cl-Ph	15	97	91
5	4-CH_3-Ph	20	93	86
6	3-NO_2-Ph	15	96	90
7	3-Br-Ph	15	96	90
8	4-OH-3-OMe-Ph	20	94	85

[a] Reaction time of step ii.

Scheme 28



Scheme 29



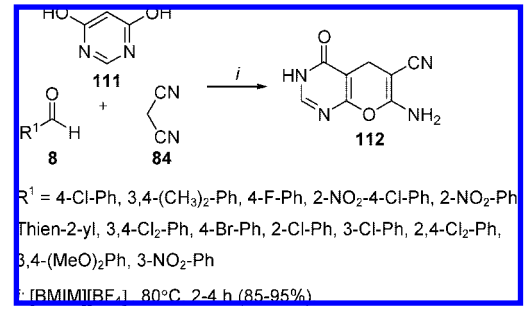
and toluene) at room temperature, but the yields found were lower than those found when ionic liquids were used (60−80%).[254]

Additionally, Song et al.[255] presented the same products **104** and the same catalytic process, except that amino-functionalized ionic liquids were utilized, as shown in Scheme 28. One noteworthy observation was that when the reactions were performed in homogeneous solutions, a higher loading capacity was achieved as a result of the lower molecular weight of the functionalized ionic liquid, and it was possible to purify the intermediates by simple extraction. The solubility and miscibility properties of ionic liquid [2-AEMIM][PF_6] are different from those of conventional ionic liquids perhaps due to hydrogen bonding. The ionic liquid was used as solvent in a molar ratio of 1:3 (reactant/IL), and it was recovered and reused seven times with no appreciable decrease in yield. To increase the scope of this protocol, a range of structurally diverse aldehydes **8** were tested, and it was found that both electron-rich and electron-deficient aromatic aldehydes proved to be suitable substrates for this reaction, providing the corresponding 4*H*-pyrans **104**. These results obtained by Song et al.[255] are similar to their previous studies,[254] likewise attesting to the increased efficiency of ionic liquids in relation to molecular solvents.

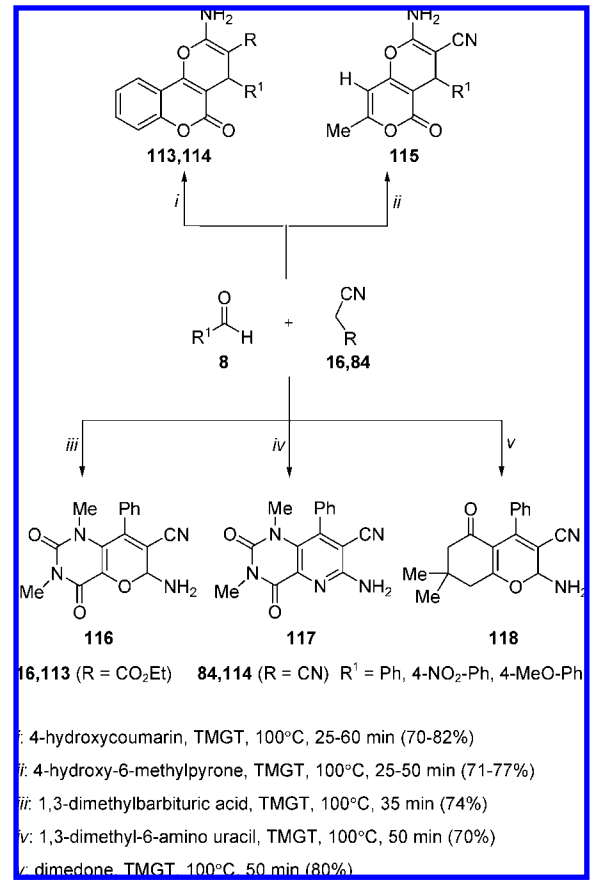
The synthesis of more complex heterocycles containing a pyran nucleus, such as pyrano[2,3-*d*]-pyrido[2,3-*d*]-pyrimidines and pyrano[3,2-*c*]benzopyran, has been attracting attention as well.[256] Recently, the use of ionic liquids in organic reactions was extended to synthesize pyrano[2,3-*d*]pyrimidine. Yu and Wang[257] reported a synthetic route using [BMIM][BF_4] to obtain pyrano[2,3-*d*]pyrimidines **110** through a condensation reaction between arylmethylidenemalononitriles **107** and barbituric acid **109** under solvent-free conditions (Scheme 29). The ionic liquid was used in a molar ratio of 1:1.5 (reactant/IL), and it was recovered and reused twice with a slight decrease in the yield of **110**. The authors reported that the reaction failed at 90 °C in molecular solvents such as toluene and 1,2-dichloroethane (10 h), showing the crucial role of the ionic liquid in these reactions.

Wang et al.[258] also synthesized pyrano[2,3-*d*]pyrimidines **112** using aromatic aldehydes **8**, malononitrile **84**, and pyrimidine-4-6-diol **111** in the ionic liquid [BMIM][BF_4] as shown in Scheme 30. The IL was used in a molar ratio of 1:26 (reactant/IL), and it was recovered and reused six times with no appreciable decrease in yield. The presence of the

Scheme 30



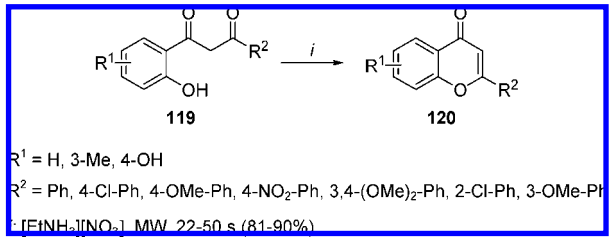
Scheme 31



ionic liquid did not improve the reaction time and product yields in comparison with the molecular solvent (dioxane). However, when this reaction was performed in dioxane, the addition of pyperidine and 4 h under reflux was necessary in order to obtain **112** (82−90% yield).[259]

Similarly, Shaabani et al.[260] reported the synthesis of pyran systems by a three-component condensation of aldehydes **8**, alkyl nitriles **16** and **84**, and either an α-hydroxy or an α-amino activated C−H acid such as 4-hydroxycoumarin, 4-hydroxy-6-methylpyrone, 1,3-dimethylbarbituric acid, 1,3-dimethyl-6-aminouracil, or dimedone in the presence of TMGT as the ionic liquid without the need for any other reactant or organic solvent (Scheme 31). The ionic liquid was used as a catalyst in a molar ratio of 1:0.1 (reactant/IL), and it was recovered and reused twice though with a decrease in yield (72%, 66%) for **113** and **114**. Experiments were also conducted to study the reaction of benzaldehyde **8**, malononitrile **84**, and 4-hydroxycoumarin at 100 °C in the absence of TMGT, where after 1 h of reaction, there was only a 12% yield of the product. However, when

Scheme 32



113−**118** were synthesized in pyridine as solvent at room temperature for 30 min, yields of ca. 80% were obtained,[261] a result superior to that obtained using an ionic liquid. Therefore, a synthetic route using the milder ionic liquids is more suitable than those that employ pyridine.

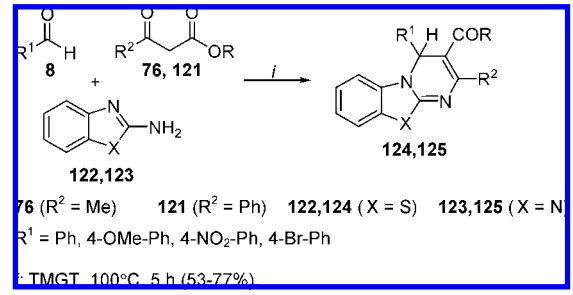
6.5. Flavones

Flavones are important naturally occurring organic compounds that possess a wide range of biological activities[262] and are used in the treatment of various diseases.[263] Different methods are used for the synthesis of flavones, including the Allan−Robinson synthesis,[264] the use of chalcones,[265] and the Wittig reaction.[266] The most common method employed to construct flavones involves a Baker−Venkatraman rearrangement. In this method, 2-hydroxyacetophenone is converted to its benzoyl ester, which in the presence of base (pyridine/KOH) gives the 1,3-diketone. The 1,3-ketones are further cyclized under strongly acidic conditions to afford the corresponding flavones.[267] Recently, the synthesis of flavones promoted by an ionic liquid catalyst, ethyl ammonium nitrate ([$EtNH_3$][NO_3]), under microwave irradiation was reported.[268] To evaluate the synthetic utility of the process, various substituted diketones **119** were subjected to the reaction under microwave irradiation (Scheme 32).[267] The reaction proceeded cleanly without the formation of any side product except water. The advantages of this method include a simple procedure and good yields. In addition, the ionic liquid was used in a molar ratio of 1:2 (reactant/IL), and it was recovered and reused twice with no appreciable decrease in yield. In another study, this reaction was performed in a molecular solvent (acetic acid) under acidic conditions (HCl) and reflux for 14 h and produced a yield of 82% of the flavone derivatives.[269] Although one cannot be certain whether it was the ionic liquid or the microwave irradiation that provided the increase in efficiency, the use of the ionic liquid proved to be a good alternative to the same procedure with a molecular solvent.

6.6. Pyrimidines and Pyrimidinones

Multicomponent condensation reactions have recently been rediscovered to be a powerful method for the synthesis of organic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component.[270] The classic version of the Biginelli three-component condensation reaction,[271] which combines an aldehyde, urea or thiourea, and an open-chain β-dicarbonyl compound under acidic conditions in ethanol, gives monocyclic 3,4-dihydropyrimidin-2-(1*H*)-ones. The Biginelli reaction has become widely used for the generation of large collections of molecules in combinatorial syntheses.[272] However, this method involves long reaction times, harsh reaction conditions, and unsatisfactory yields. Shaabani et al.[81b] established the use of ionic liquids in a modified

Scheme 33

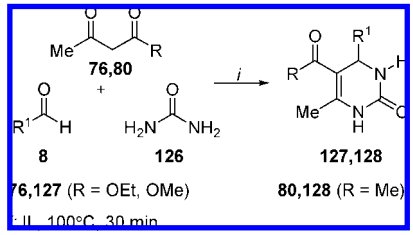


method of the Biginelli reaction. The synthetic protocol entails the condensation of aldehydes **8**, β-ketoesters **76** or **121**, and either 2-aminobenzothiazole **122** or 2-aminobenzimidazole **123** in the presence of TMGT as an ionic liquid at 100 °C (Scheme 33). The ionic liquid was used in a molar ratio of 1:0.1 (reactant/IL), and it was recovered and reused three times with a slight decrease in yield. The reaction presumably proceeds in two steps: the condensation of **8** and **76** or **121** by the standard Knoevenagel reaction, producing 3-benzylidene-2,4-pentenedione; then, reaction of 2-aminobenzothiazol **122** or 2-aminobenzimidazole **123** with the Knoevenagel product through a Michael addition resulting in a product that, after cyclization, affords 4*H*-pyrimido[2,1-*b*]benzazoles **124** or **125**. The reaction proceeds efficiently with both electron-withdrawing and electron-releasing 4-substituted benzaldehydes **8**. It is important to note that in the absence of TMGT, the yield of the reaction decreased by up to 25% after 5 h. Furthermore, when the reaction was carried out in H_2SO_4 as catalyst and in ethanol under reflux (18 h), the yields for **124** and **125** were between 40% and 60%.[273]

In addition, Deng and Peng[274] reported the use of an ionic liquid as catalyst for the Biginelli condensation reaction under solvent-free conditions (Table 14). The synthetic route to obtain pyrimidinones **127** and **128** consists of the condensation of aldehydes **8**, β-ketoesters **76** and **80** and urea **126** in the presence of an ionic liquid at 100 °C (Table 14). It can be seen that all starting materials reacted very well, and the yields achieved from the aromatic aldehydes **8** with electron-donating substituents were slightly higher than those from aromatic aldehydes **8** with electron-withdrawing substituents. For the sake of comparison, toluene was added into the reaction system. The reaction was refluxed at 100 °C for 2 h, and the yield (77%) was lower. Entry 1 (Table 14) shows that the reaction was fruitless in the absence of an ionic liquid.

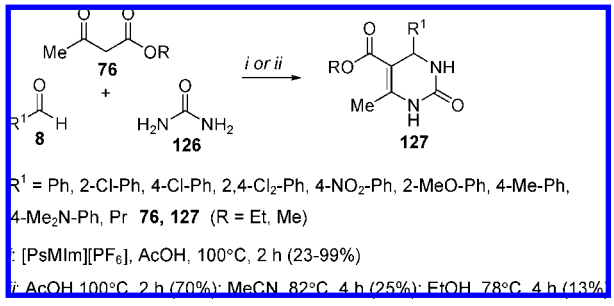
Wang et al.[275] developed a polymer-supported ionic liquid catalyst for the synthesis of pyrimidinones **127**. The catalyst system was produced by immobilizing the catalyst on Merrifield resin to obtain PsMim-based ionic liquids. The pyrimidinones **127** resulted from the condensation of an aldehydes **8**, β-ketoesters **76**, and urea **126** in the presence of an ionic liquid at 100 °C (Scheme 34). The ionic liquid was recovered and reused four times with no appreciable decrease in yield (97%, 94%, 90%, and 91%). The authors concluded that the use of recoverable, polymer-supported ionic liquids as catalysts provides a simple and effective method for the Biginelli reaction performed with aromatic aldehydes **8**. Aromatic aldehydes **8** with electron-donating groups favored this Biginelli condensation. In contrast, aromatic aldehydes **8** with electron-withdrawing substituents gave somewhat lower, yet still good, yields (74−91%). To compare with a molecular solvent, the reaction was carried

Table 14. Synthesis of Pyrimidinones from Biginelli Condensation Reaction

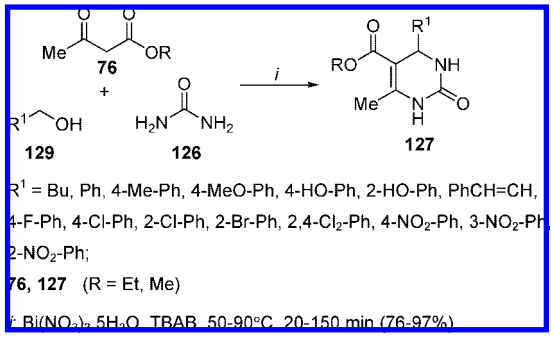


Entry	IL (mmol)	R^1	yield (%)
1	none	Ph	0
2	[BMIM][BF_4] (0.05)	Ph	85
3	[BMIM][BF_4] (0.1)	Ph	92
4	[BMIM][BF_4] (0.2)	Ph	95
5	[BMIM][BF_4] (0.1)	4-OMe-Ph	95
6	[BMIM][BF_4] (0.1)	4-Cl-Ph	96
7	[BMIM][BF_4] (0.1)	4-NO_2−Ph	90
8	[BMIM][PF_6] (0.1)	Ph	94
9	[BMIM][PF_6] (0.1)	4-OMe-Ph	98
10	[BMIM][PF_6] (0.1)	4-Cl-Ph	98
11	[BMIM][PF_6] (0.1)	4-NO_2-Ph	92
12	[BMIM][BF_4] (0.1)	Pentyl	93
13	[BMIM][BF_4] (0.1)	Ph	99
14	[BMIM][BF_4] (0.1)	4-NO_2-Ph	92
15	[BMIM]BF_4 (0.1)	4-NO_2-Ph	77
16	[BMIM][Cl] (0.1)	Ph	56
17	[Bu_4N][Cl] (0.1)	Ph	0

Scheme 34



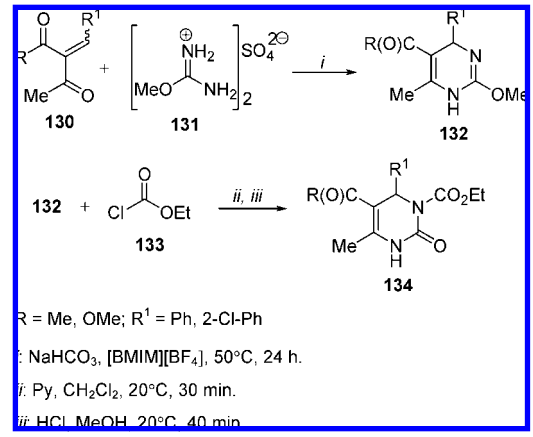
Scheme 35



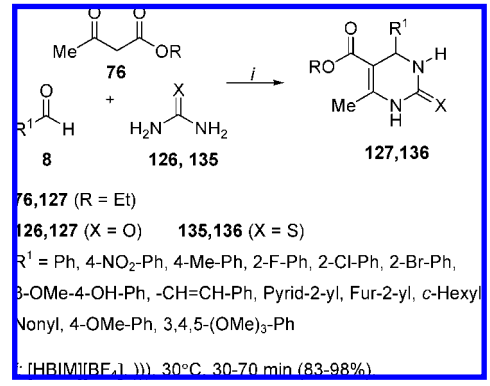
out in EtOH, CH_3CN, and AcOH without a catalyst, and the yields were lower. The results are summarized in Scheme 34.

Khosropour et al.[276] employed 3.5 mol% of TBAB to synthesize pyrimidinones **127**. This Biginelli reaction employed primary alcohols **129** (instead of aldehydes), β-ketoesters **76**, and $Bi(NO_3)_3$. The one-pot oxidation−cyclocondensation reaction is performed without the isolation of an intermediate aldehyde (Scheme 35). The treatment of primary benzyl alcohols **8**, carrying either electron-withdrawing or electron-donating groups, afforded **127** in high yields and short reaction times. Another important aspect was that various functionalities, such as ether, halide and nitro, survived under these reaction conditions.[276] The authors carried out the same reaction in acetonitrile as solvent, where the reaction time was 40 min, and the yield was about 80%.

Scheme 36



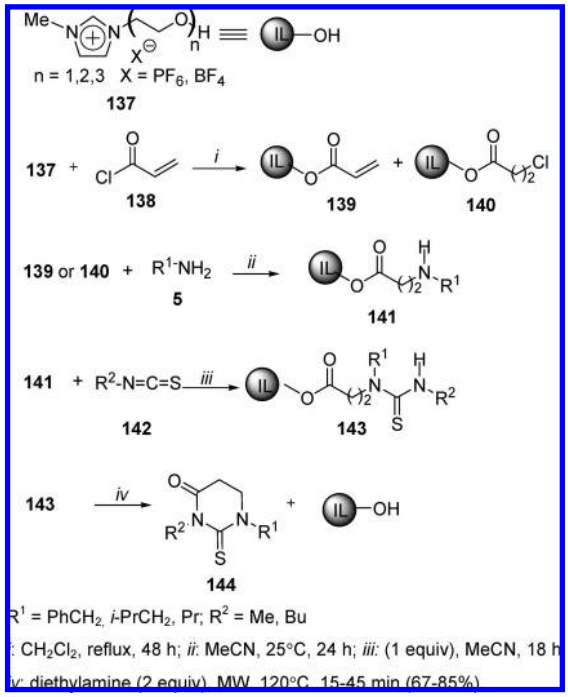
Scheme 37



Zlotin et al.[277] demonstrated the application of ionic liquids in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones **132** using [BMIM][BF_4]. The reaction consisted of the condensation between 2-arylidenes **130** and *O*-methylisourea sulfate **131** (Scheme 36). The results of this study demonstrated that the condensation process was substantially affected by the ionic liquid. The authors affirmed that the product from the first step undergoes partial isomerization under the reaction conditions in the presence of $NaHCO_3$ and in an ionic liquid medium in a molar ratio of 1:0.2 (reactant/IL), which is more polar than DMF.[278] This compound is then transformed into the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones **134** by regioselective N-alkoxycarbonylation and O-demethylation of **132**.[277] When the same procedure was performed with the molecular solvent DMF using K_2CO_3 as base, the products were only attained after 16 h at room temperature.[279] [BMIM]BF_4 therefore improved the reaction by dramatically reducing the reaction time.

Srinivasan et al.[280] reported the use of an ionic liquid combined with ultrasound irradiation for the synthesis of the 3,4-dihydropyrimidin-2-(1)-ones **127** and **136** from the Biginelli reaction in excellent isolated yields and short reaction times (Scheme 37). The synthetic route entails the condensation of an aldehydes **8**, β-ketoesters **76**, and urea **126** or thiourea **135** in the presence of the ionic liquid in a ratio of 1:1 (reactant/IL) under ultrasound, resulting in pyrimidinones **127** or **136** (Scheme 37). The authors observed

Scheme 38

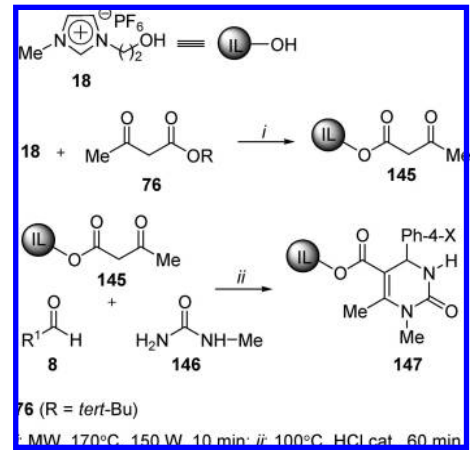


that the reaction did not come to fruition even after several hours of sonication in molecular solvents such as acetonitrile, ethanol, THF, and dichloromethane in the place of the ionic liquids. It is thereby evident that the synergic effect of ultrasound combined with the ionic liquid as the reaction media promoted this MCR at room temperature in the absence of any added catalyst.

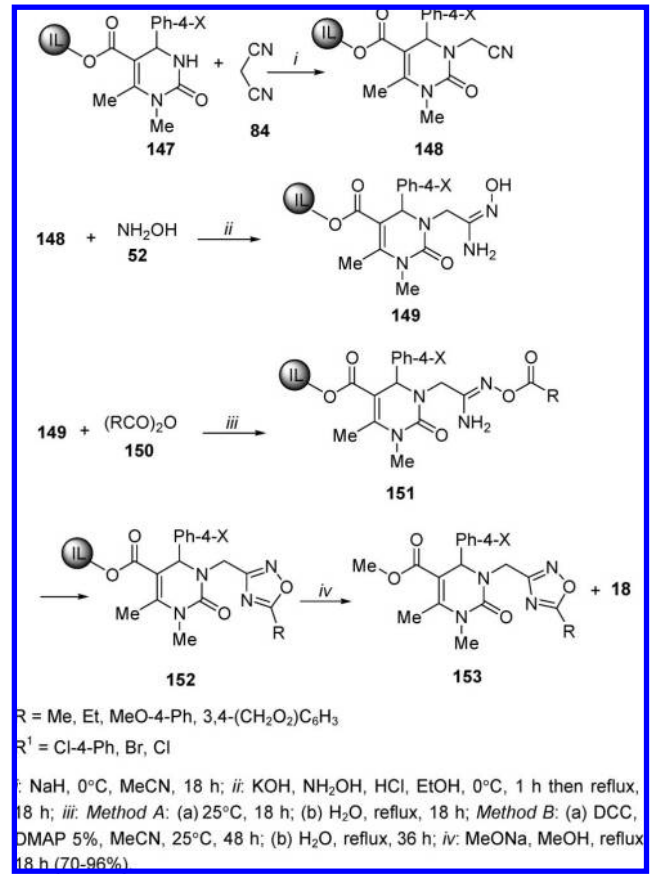
Another multicomponent reaction performed in ionic liquid to obtain 2-thioxotetrahydropyrimidin-4-(1*H*)-ones **144** was published by Bazureau et al.[281] The methodology employs microwave irradiation and a matrix of PEG-ILPs used for an ionic liquid phase organic synthesis. To use PEG-ILPs as tools in "liquid phase organic synthesis", the author chose to investigate the 2-thioxo-tetrahydropyrimidinones moiety **144** as a new heterocyclic scaffold. The 2-thioxotetrahydropyrimidin-4(1*H*)-one can be built from the intermediate **141** and isothiocyanates **142**. Compound **141** was obtained from the reaction of a primary amine **5** and compound **139** or **140**, formed from the reaction of β-dielectrophile **138** with IL **137** (Scheme 38).

The novel use of PEG-ILPs in liquid-phase organic synthesis offers considerable advantages because side products are removed by a single extraction and with washings from the cleaved IL phase. Continuing their work in this area, Bazureau et al.[282] have developed the synthesis of N-3 functionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) **153** (Scheme 40) with a 1,2,4-oxadiazole group via the three-component Biginelli condensation without solvent, according to the "ionic liquid-phase organic synthesis" (IoLiPOS) methodology (Scheme 39). In this paper, the authors reported that the protocol involved the attachment of the 3,4-DHPM heterocycles **147** on the ILP bound acetoacetates **76** by a solventless, one-pot, three-component condensation. Then, the 3,4-DHPM **147** were functionalized with 1,2,4-oxadiazole using two convergent methods either from aliphatic carboxylic anhydrides (**150**) or from aromatic carboxylic acids, as reactional sequence shown in the Scheme 40. Due to the high loading capacity of the ILP, in many cases the use of

Scheme 39



Scheme 40

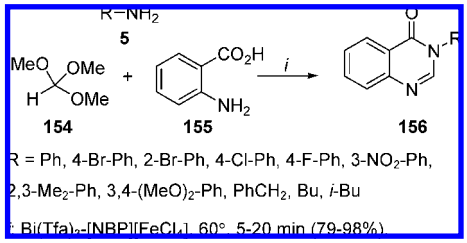


a large excess of reactants was avoided, which is generally a disadvantage to the conventional solid-phase synthesis methods.

6.7. Quinazolines

4(3*H*)-Quinazolinones have emerged as an important class of nitrogenated heterocycles attracting significant synthetic interest because of their pharmacological and therapeutic properties.[283] There are several methods for the synthesis of 4(3*H*)-quinazolinones.[284] One method developed by Khosropour et al. is the immobilization of Lewis acids in ionic liquids[285] to obtain 4(3*H*)-quinazolinone **156** by the condensation reaction of anthranilic acid **155**, trimethyl orthoformate **154**, and primary amines **5** in the presence of a catalytic amount of $Bi(Tfa)_3$ in [NBP][$FeCl_4$] as a room-

Scheme 41

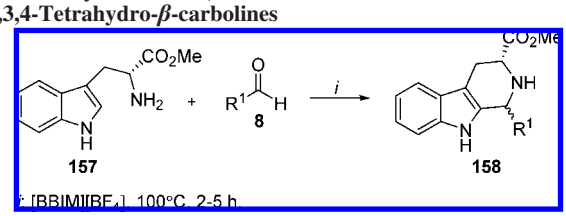


temperature ionic liquid (Scheme 41). The reactions were carried out at 60 °C for 5−20 min by reacting a 1:1.2:1.2 molar ratio mixture of **154**, **155**, and **5**, respectively, in the presence of 5 mol % $Bi(Tfa)_3$ in $[NBP][FeCl_4]$ to give the desired products in high to excellent yields (79−98%). The ionic liquid was recovered and reused three times with no appreciable decrease in yield. Interestingly, it was observed that the combination of $Bi(Tfa)_3$−$[NBP][FeCl_4]$ was essential for this transformation. Attempts to carry out the reaction in the absence of either of these catalysts did not yield the products, and only the starting materials were isolated. When this reaction was performed in the molecular solvent EtOH, the addition of NaOH and 30% H_2O_2 under reflux for 1 h was necessary to obtain 75% yield of the product.[286]

6.8. β-Carbolines

The β-carboline core is also of interest, being an important pharmacophore in numerous biologically active compounds.[287a,b] The Pictet−Spengler reaction is a commonly used method for the synthesis of tetrahydro-β-carbolines.[287c] The Pictet−Spengler products are epimer compounds because the stereochemistry of one stereogenic center in the reactant (amino acid) is kept in the product and the second stereogenic center is derived from the prostereogenic aldehyde. Thus, in the typical Pictet−Spengler reaction, a mixture of cis and trans diatereoisomers is expected. Normally, strong Brønsted/Lewis acids ranging from catalytic to stoichiometric amounts are employed to accomplish the Pictet−Spengler reaction. In this context, many researchers have experienced the need for an efficient methodology for the synthesis of β-carboline libraries and have shown interest in the possibility of carrying out the Pictet−Spengler reaction in ionic liquids. Hence, Joshi et al.[288] reported the synthesis of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines **158** by a Pictet−Spengler cyclization in $[BBIM][BF_4]$. The synthetic procedure was based on the Pictet−Spengler condensation of D-tryptophan methyl ester **157** and benzaldehydes **8** in different imidazolium-based ionic liquids in the presence of TFA as an acid catalyst (Table 15). The diastereomeric ratio cis/trans found for products **158** is described in Table 15. During the course of screening a variety of reaction conditions such as different ionic liquids, reaction temperatures, and reaction times, the authors found $[BBIM][BF_4]$ to be superior to other ionic liquids. They also found that the use of TFA as an acid catalyst was in fact not necessary for an efficient Pictet−Spengler cyclization in ionic liquid.[289] In the methodology chosen, the ionic liquid was used in a molar ratio of 1:4 (reactant/IL), and it was recovered and reused twice with no appreciable decrease in yield (88% and 86%). It is important to mention that, from the results known from the literature,[290] the Pictet−Spengler cyclization catalyzed by TFA in a molecular organic solvent, for example, methylene chloride, gave the corresponding **158** in 62% yield after stirring at

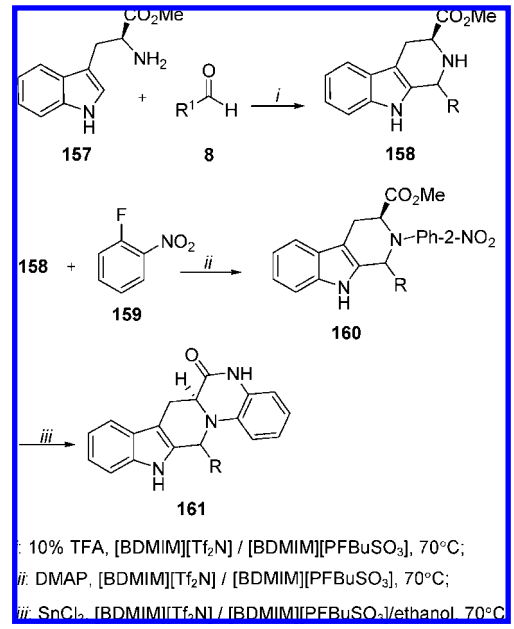
Table 15. Synthesis of 1,3-Disubstituted 1,2,3,4-Tetrahydro-β-carbolines



entry	R^1	time (h)	yield (%)	diastereomeric ratio (cis/trans)[a]
1	Ph	2.0	90	1:0.9
2	3-OCH_2-O-4-Ph	4.0	70	1:0.8
3	2-F-Ph	2.0	85	1:0.7
4	2-Cl-Ph	2.0	82	1:1
5	2-NO_2-Ph	2.5	84	1:0.6
6	4-F-Ph	2.0	75	1:0.7
7	4-Cl-Ph	4.0	80	1:1
8	4-NO_2-Ph	2.0	75	1:0.6
9	4-MeO-Ph	5.0	82	1:0.9

[a] Cis/trans refers to the relative position between R^1 and the CO_2Me group.

Table 16. Synthesis of Fused Tetrahydro-β-carbolinequinoxalinones



entry	R	ionic liquid	time (h)	yield (%)
1	4-OMe-Ph	$[BDMIM][Tf_2N]$	1.5	64
2	Ph	$[BDMIM][Tf_2N]$	0.6	66
3	4-Cl-Ph	$[BDMIM][Tf_2N]$	0.7	71
4	2-F-Ph	$[BDMIM][PFBuSO_3]$	0.9	61
5	naphth-2-yl	$[BDMIM][PFBuSO_3]$	1.5	61
6	4-Me-Ph	$[BDMIM][PFBuSO_3]$	1.0	62

room temperature for 4 days, in comparison to 2−5 h reaction time and 82% yield from the ionic liquid method.

On the other hand, Chu et al.[291] demonstrated the synthesis of fused tetrahydro-β-carbolinequinoxalinones **161** in the ionic liquids $[BDMIM][Tf_2N]$ and $[BDMIM][PFBuSO_3]$ (Table 16). Three reactions were incorporated into the synthesis: the Pictet−Spengler condensation[287c,288] used in step i, the nucleophilic aromatic substitution in step ii, and the cyclization-upon-reduction reaction in step iii (Table 16). The synthesis of quinoxalinones **161** in ionic liquids involved

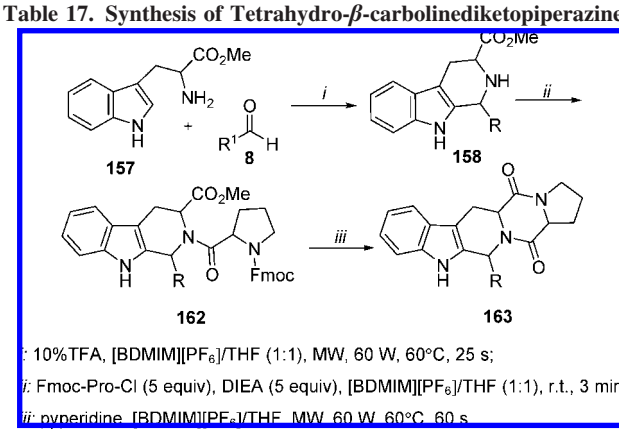
the direct coupling of 2-nitrofluorobenzene **159** with sterically hindered and less reactive tetrahydro-β-carbolines **158**, and there was no apparent preference for a particular isomer.[288] It can be noted that the approach of using ionic liquid as the reaction medium was effective with sterically hindered and substituted tetrahydro-β-carbolines **158**.[292] The last step, a cyclization-upon-reduction reaction, was carried out without the aid of additional bases. The results indicate that under a standard reduction by tin chloride and the subsequent intramolecular cyclization, the desired tetrahydro-β-carbolinequinoxalinones **161** were readily formed as sole products in moderate overall isolated yields (34−55%). The IL was used for all steps and improved the yields (Table 16). The similarity of these reactions with those previously cited[270,272] once more sustains the idea that ionic liquids are more efficient compared with molecular solvents.[289]

Chu and Yen[293] also reported the total synthesis of tetrahydro-β-carbolinediketopyperazines **163** in [BDMIM][PF_6] in a molar ratio of 1:1 (reactant/IL). Three reactions were incorporated into the synthetic table: the Pictet−Spengler condensation used as the first step (i),[291] the Schotten−Baumann acylation as the second step (ii), and an intramolecular ester amidation for the last step (iii). The Schotten−Baumann itself is a fast reaction, and therefore, microwaves were only used in the first and last steps to speed up the synthesis of **163** (Table 17). As shown in the table, the Schotten−Baumann reaction involves three steps, which employ aldehydes **8**, TFA, MW, Fmoc-Pro-Cl, DIEA, and, in the last step, pyperidine. The authors noted that if the same Pictet−Spengler reaction was carried out in conventional solvents such as dichloromethane, 7−8 h were required to complete the reaction at room temperature.[293]

6.9. Dioxanes

The acid-catalyzed condensation of olefins with aldehydes, known as the Prins reaction, is an important carbon−carbon bond forming reaction in organic synthesis.[294] The major products of the classical Prins reaction are normally 1,3-diols, 1,3-dioxanes, unsaturated alcohols, and the products obtained from the acid-catalyzed polymerization of olefins.[295] 1,3-Diols are particularly important building blocks in the total synthesis of various bioactive natural products.[296] The most simple and straightforward method for the synthesis of 1,3-diols is the addition of olefins to paraformaldehyde in the presence of acid catalysts. Generally, Lewis acids or Brønsted acids are employed in both catalytic and stoichiometric amounts to promote this transformation.[297,298] Accordingly, Yadav et al.[299] reported the synthesis of 1,3-dioxanes **166** using a catalytic amount of indium tribromide in [BMIM][PF_6]. A variety of styrenes **164** reacted smoothly with paraformaldehyde **165** to give the corresponding 1,3-dioxanes **166** in excellent yields. In all cases, the reactions proceeded efficiently at 25 °C with high selectivity. The best results were achieved when the reactions were carried out at room temperature for 3.5−6.5 h in the presence of 10% indium tribromide in ionic liquids (Scheme 42). The ionic liquid was used in a molar ratio of 1:5 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in yield. Compared with conventional solvents, enhanced reaction rates, improved yields, and high selectivity were the main advantages displayed by ionic liquids. For example, the treatment of *trans*-stilbenes **164** with **165** in the presence of 10 mol % indium tribromide in [BMIM][PF_6] for 5.5 h afforded the corresponding 4,5-diphenyl-1,3-dioxane **166** in 90% yield with trans selectivity whereas the same reaction in dichloromethane after 8.0 h gave the product in 70% yield as cis and trans isomers in a molar ratio of 2:8.[300]

Table 17. Synthesis of Tetrahydro-β-carbolinediketopiperazines

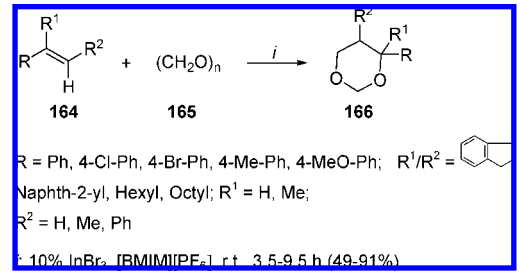


Room Temperature						
		reaction time				
entry	R	step 1 (h)	step 2 (min)	step 3 (h)	yield (%)	diateroisomeric cis/trans ratio[a]
1	Et	2	3	2	41	27:73
2	Pr	2.5	3	2	30	68:32
3	Bn	2.5	3	2	20	9:91
4	4-Me-Ph	2	3	2	35	67:33
5	4-OMe-Ph	3	3	2	30	15:85
6	4-F-Ph	2	3	2	25	59:41

Microwave						
		Reaction Time				
entry	R	step 1 (s)	step 2 (min)	step 3 (s)	yield (%)	diateroisomeric cis/trans ratio[a]
1	Et	25	3	60	69	41:59
2	Pr	25	3	60	56	66:34
3	Bn	25	3	60	62	10:90
4	4-Me-Ph	25	3	60	55	38:62
5	4-OMe-Ph	25	3	60	49	42:58
6	4-F-Ph	25	3	60	49	65:35

[a] The stereochemistry of the diasteroisomers was determined by ^{13}C NMR. The diastereoisomer fractions were measured by C18-HPLC. In a pair of diastereoisomers, the second number represents the trans isomer in the table.

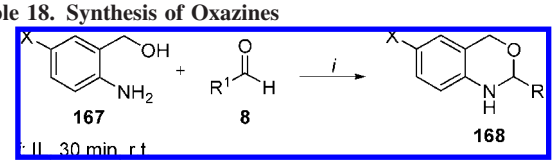
Scheme 42



6.10. Oxazines

1,2-Oxazines are heterocycles of pharmacological relevance and represent useful synthetic building blocks. They have been used, for instance, as intermediates during the synthesis of glycosidase inhibitor analogues[301] and functionalized pyrroles.[302] Many syntheses of 1,2-oxazines rely on hetero-Diels−Alder reactions of alkenes with ene−nitroso

Table 18. Synthesis of Oxazines



entry	X	R^1	IL[a]	yield (%)
1	H	Ph	1, 2, 3, 4, 5	95, 89, 98, 98, 98
2		4-F-Ph	3	97
3		4-CF_3-Ph	3	95
4	Cl	Ph	1, 2, 3, 4, 5	96, 84, 99, 98, 97
5		4-F-Ph	3	99

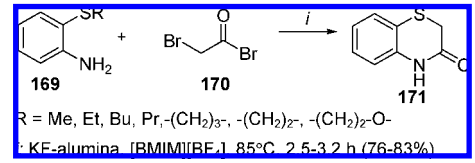
[a] (1) 8-Ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate; (2) 8-Methyl-1,8-diazabicyclo[5,4,0]-undecenium trifluoromethanesulfonate; (3) [EMIM][CF_3SO_3];(4) [BMIM][BF_4]; (5) [BMIM][PF_6].

compounds, derived from α-haloximes[303] or on hetero-Diels−Alder reactions of dienes with nitroso compounds.[301,303e] Other methods rely on cyclization of alkenyl-substituted oximes in the presence of NBS,[304] diphenyldiselenide,[305] or an acid[306] or through photochemical activation.[307] In addition, 1,2-oxazines have been prepared by base-mediated cyclization of γ-chloroximes[308] and γ-sulfonyloximes.[309]Other syntheses rely on the Lewis acid catalyzed reaction of allenoximes,[310] the acid-catalyzed cyclization of cyclopropyloximes,[311] or the cyclization of γ-nitroketones.[312] Kitazume et al.[313] introduced the use of ionic liquids in the synthesis of oxazines **168** from the reaction of benzaldehydes **8** with 2-aminobenzyl alcohols **167** as shown in Table 18. Ionic liquid was used in a molar ratio of 1:6 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in yield. Usually, the synthesis of these heterocycles is carried out in polar organic solvents (such as THF, DMF, or DMSO), and after quenching with water, the products are extracted with organic solvents. When tetrahydrofuran was used as a solvent in the reaction above, the product was obtained an excelent yield (91%), but it was not easy to separate the solvent and the product by direct distillation. When an ionic liquid was utilized to perform the same reaction, the product was separated by extraction with diethyl ether, and the ionic liquid was recovered. On the other hand, when this reaction was performed in CH_2Cl_2 at room temperature with addition of $BF_3 \cdot OEt_2$ for 12 h, the yield was 73%.[313]

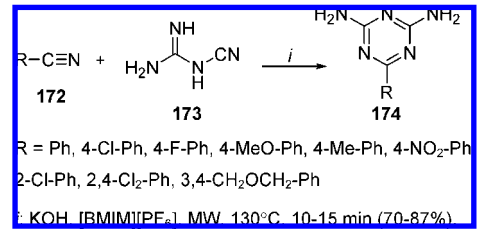
6.11. Benzothiazines

1,4-Benzothiazine is a molecule of interest to chemists and biologists both, being a subunit of various tissues such as mammalian hair and feathers and also a precursor in many synthetic transformations leading to biologically active heterocyclic molecules.[314] Various methods have been reported for the synthesis of 1,4-benzothiazine such as synthesis from 2-aminothiophenol[315] by a reductive cyclization of α-(4-nitrophenylthio) acids[316] and 2-aminophenyl disulfides.[317] While investigating the use of ionic liquids in cyclization reactions for the synthesis of macrocyclic chelating agents, Tandon et al.[318] observed the transformation of alkylsulfanylphenylamines **169** into 3-oxo-1,4-benzothiazines **171**, found to be the sole product after spectroscopic analysis (Scheme 43). The advantage of this method was the ease product separation provided by the solid-supported heterogeneous base. Interestingly, the alkylsulfanylamines **169**, which have smaller alkyl groups, were converted to benzothiazines **171**in a shorter time and in higher yields

Scheme 43



Scheme 44

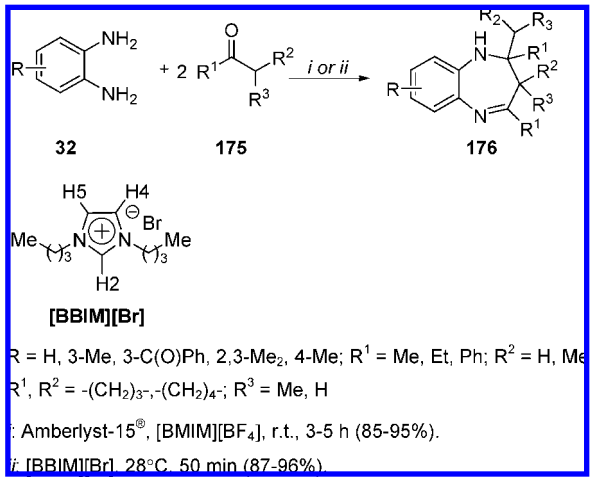


compared with those of larger alkyl groups. This may have been due to the steric factor involved at the time of cyclization with the nucleophilic substitution at the thio group. The ionic liquid was used in a molar ratio of 1:10 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in yield. This transformation in molecular solvents is rarely described in the literature. One of the few examples employs DMSO as a molecular solvent, under reflux for 30−40 min, and the yields found were 62−72%.[319]

6.12. Triazines

1,3,5-Triazines are a class of attractive compounds in the modern chemical industry.[320a] They are widely employed as flame-retardant additives in common resins[320b] or pivotal structural units in fire-resistant polymers[320c] Chemically modified 6-aryl-2,4-diaminotriazines have also been reported as new ligands with potential multicoordination modes,[320d] cross-linkers in coatings,[320e] vermin-repellent microcapsules with slow-release potentiality,[320f] corrosion-resistant agents on metal surfaces,[320g] and candidates for antiulcerous[320h] and allergy-inhibiting drugs.[320i] The synthesis of 6-aryl-2,4-diaminotriazines typically involves the condensation of arylnitriles with dicyandiamide in an alcohol solution in the presence of a strong base.[321,322] Unfortunately, these transformations have traditionally suffered from long reaction times, for example, 24 h at 140 °C with yields between 53−75%.[321a] Thus, Song et al.[323] reported a method using ionic liquids to produce substituted diaminotriazines **174**. The reaction occurred by cyclization of dicyandiamide **173** with various arylnitriles **172** using microwave irradiation (Scheme 44). Employing computer-aided control of dielectric heating, the desired products **174** were formed efficiently, and the reaction times were shortened from 15−24 h to 15 min or even less. The ionic character of the ionic liquids provides excellent coupling capability with microwave irradiation. However, for organic reactions performed in ionic liquids under consecutive microwave irradiation, overheating is an inevitable problem because of the nonvolatile nature of such solvents.[323] In this method, the ionic liquid was used in a molar ratio of 1:1 (reactant/IL), and it was recovered and reused five times with no appreciable decrease in the yield (87% to 83%) of **174**.

Scheme 45



7. Synthesis of Seven-Membered Heterocycles: Diazepines

Benzodiazepines are an important class of bioactive molecules.[324] Despite their wide range of pharmacological activity and industrial and synthetic applications, the synthesis of benzodiazepines has received little attention.[325] Methods reported in the literature for the synthesis of 1,5-benzodiazepines, many of which are recent, include condensation reactions of 2-phenylenediamine with α,β-unsaturated carbonyl compounds,[326] β-haloketones,[327] or ketones in the presence of BF_3-etherate,[328] $NaBH_4$,[329] polyphosphoric acid, or SiO_2,[330] MgO/PCl_3,[325a] $Yb(OTf)_3$,[325b] or Al_2O_3/P_2O_5 or AcOH under microwave irradiation.[331] Many of these processes suffer from one of a number of limitations. Therefore Yadav et al.[332] investigated the synthesis of 1,5-benzodiazepines **176** using ionic liquid from the treatment of 2-phenylenediamines **32** with different ketones **175** using Amberlyst-15 immobilized in $[BMIM][BF_4]$ (Scheme 45). The advantage of ionic liquids as solvent in a molar ratio of 1:10 (reactant/IL) for this transformation was the ease of the catalyst/substrate separation due to the heterogeneous catalyst. In addition, the ionic liquid was recovered and reused four times with no appreciable decrease in yield (95% to 81%). The authors performed the reactions in polar organic solvents such as DMF and *N*-methylpyrrolidine to compare the efficiency of ionic liquids. However, the reaction did not come to fruition in these solvents even under heating (75−80 °C) in the presence of an ion-exchange resin. The products were obtained in low to moderated yields (45−60%) when the reactions were carried out in chloroform in the presence of acid resin. The advantages of ionic liquids over conventional solvents in this case were enhanced reaction rates, improved yields, and high selectivity. For example, the treatment of 2-phenylenediamines **32** with 2-butanone **175** in the presence of acid resin in ionic liquid for 3−4 h afforded the corresponding **176** in 88% yield with only a trace amount of the other regioisomeric product (5%), whereas the same reaction in chloroform for 7 h gave the regioisomeric products in 60% yields in a 1:1 molar ratio. Srinivasan et al.[333] also developed a regioselective synthesis of 1,5-benzodiazepines **176** in [BBIM][Br]. 2-Phenylenediamines **32** was reacted with both acyclic and cyclic ketones **175** in [BBIM][Br] in the absence of any other catalyst (Scheme 45). The enhanced reactivity for the synthesis of the benzodiazepines **176** in [BBIM][Br], even in the absence of a catalyst, was attributed by the authors to the inherent Lewis acidities of the H2, H4, and H5 hydrogens of the imidazolium cation in [BBIM][Br]. The ionic liquid acts not only as a solvating medium but also as a promoter for the reaction resulting in the twin advantages of allowing room-temperature conditions and not requiring a catalyst.[333] In all cases, the ionic liquid was used in a molar ratio of 1:1 (reactant/IL), and it was recovered and reused three times with no appreciable decrease in yield. The advantages of the ionic liquid over molecular solvents are once again evident, as corroborated by Yadav et al.[332]

8. Green Aspects of Ionic Liquids

Recently, ILs have gained considerable attention in several branches of the chemical industry as potential "green" substitutes for conventional organic solvents.[334,335] The "green" aspect of ILs is mainly derived from their undetectable vapor pressure, flammability, and toxicity because this decreases the risk of exposure and loss of solvent by evaporation, thereby reducing air pollution. However, these green credentials are not sufficient for design of sustainable chemical products, and it is necessary to refer to the concept of ecotoxicological risk profiles, which comparatively assess substances according to the five risk indicators: release, spatiotemporal range, bioaccumulation, and biological activity.[336] Concerning the release of and from ionic liquids, applications and processes have to be designed to take into account the toxic potential of the substances employed. Currently, this seems to be possible, especially when ILs are used under highly controlled conditions in chemical production facilities. The biodegradability of ILs has focused on making the cation more biodegradable. Because of the need for hydrophobic ILs, it seems to be of primary importance to develop anions that introduce sufficient hydrophobicity but are at the same time biodegradable. Even if high bioaccumulation and toxicity might be observed for the parent compound, its ready degradation, starting in wastewater treatment facilities, would decrease the joint bioaccumulation of the parent compound and the transformation products, and critical body residues would not be reached.[336] As their popularity with industrial chemists increases, the probability that ILs will find their way into water courses through effluent discharges or accidental spills will also increase, and they may affect the aquatic environment for a long time because of their poor biodegradability. In addition to current studies on wastewater treatment methods and biodegradation, the toxicity of the degradation products should be investigated to make sure that they are less toxic than the original products. The knowledge we have on IL toxicity, which has been argued to be dominated by their bioaccumulation potential, already allows for a T-SAR directed design for low toxicity.[336] The key factor will be low anion and cation lipophilicity. If, however, lipophilicity in the form of low water solubility is a technical requirement, a design for biodegradability could resolve the conflict between safety and technical requirements. According to Jastorff et al.,[337] the toxicity of ILs is roughly driven by the head group, the side chain, and the anion. Currently, the biological effects of ILs have resulted in increasing reports, which have dealt mainly with the influence of the alkyl side chain length of various ILs head groups. Pernak et al.[338–342] pointed out that their antimicrobial activity increased with increasing alkyl chain length on pyridinium, imidazolium, and quaternary ammonium salts. Similar phenomena were also observed for enzyme acetylcholinesterase,[343] the marine

bacterium *Vibrio fischeri*,[344,345] mammalian cells,[344] human cell HeLa cells,[346] and higher organisms, including the soil nematode *Caenorhabditis elegans*,[347] as well as the freshwater snail *Physa acuta*.[348] However, with respect to the influence of anions, no consistent conclusion has been obtained from previous investigations. Some studies have reported that varying the anion had minimal effects on the toxicities of several pyridinium and imidazolium compounds and indicated that the toxicity of ILs was largely driven by the alkyl chain branching and hydrophobicity of the cation.[340,344,349,350] In the meantime, others have suggested that the counteranion contributed significantly to their toxicity.[346,351,352] In particular, some ILs with fluorine-containing anions were suggested to be relatively toxic because the anions were hydrolyzed to fluoride in the aqueous solution and the fluoride had a toxic effect.[346,351] However, in-depth studies on this hydrolysis of fluorine-containing anions and their effect on the toxicity were insufficient to explain the inhibitory effect of ILs. The toxicity of ILs towards aquatic organisms, such as fish and invertebrates, has been extensively studied,[337,349,352,353] but the influence of ILs on freshwater green algae has rarely been.

The relatively high solubilities of the ILs in the water phase, the low EC_{50} values obtained for some of them and their poor biodegradability (which makes them persistent pollutants) have important environmental consequences and should be taken into account for the design of processes that use ILs. To avoid the potential contamination of the aqueous phase with ILs, several strategies should be planned. Firstly, it is important to improve the processes, minimizing IL leaching to the aquatic media. There is also next to no knowledge on sublethal and chronic effects of ILs on biological organisms. However, this is of limited relevance as long as only small volumes of readily biodegradable ILs are released to the environment. If large volumes of refractory ILs were to be released, the question of sublethal and chronic effects would of course quickly be relevant. Summing up, the structural variability of ionic liquids provides substances that have a low risk regarding each of the five risk indicators.[336] Therefore, there is a good chance that we will see a sustainable ionic liquid with an excellent risk profile for a defined technical application, which is itself in line with sustainable development. However, the reverse is also possible, if no care is taken to avoid unfavorable risk profiles. A start with analyzing the life cycle of an ionic liquid has already been made,[354] and future studies should take a more holistic view on products and processes.

9. Economic Perspectives for Ionic Liquids

Ionic liquids offer the potential for ground-breaking changes to synthesis routes and unit operations in the chemical industry. There is rapidly growing worldwide scientific and commercial interest in ionic liquids, demonstrated by the accelerating number of ionic liquid publications and patents. The prospects for ionic liquid use are vast. The literature and patents describe numerous applications such as catalysis with increased rates and yields, less complex and more energy-efficient separations, and solvents that may reduce environmental impacts for commercial processes. The substantial benefits described in the literature and patents should promote rapid ionic liquid technology adoption. However, despite their significant benefits and potential for numerous applications in the chemical industry, their development has remained mostly in the discovery stages of research based on understanding the fundamental relationships between structure, properties, and reactivity.

Ionic liquid applications that have broad chemical industry impact only become a reality when the economies of these applications are favorable and well understood. The costs of commercially using ionic liquids in industrial processes are unknown. Therefore, comprehensive cost−benefit analysis of direct and indirect advantages and risks of ionic liquid processes versus conventional technologies should be performed and published. Beyond a simple evaluation of the cost−benefit of ionic liquids in a specific process, these assessments should include estimates of long-term indirect benefits of ionic liquid use, such as water savings, energy savings, environmental benefits, the ability of an industry to be ahead of the market in terms of meeting or exceeding emissions standards, and other externalities that are not recognized when simply measuring the benefits of ionic liquids as a substitute for molecular solvents. This would provide a more comprehensive representation of how ionic liquids measure up to traditional organic solvent and catalytic systems.

Uncertainty of ionic liquid cost and availability for industrial chemical applications increases the risks associated with ionic liquid processes. Even if the performance of ionic liquid processes is vastly superior, the costs associated with small losses of expensive ionic liquid inventory can quickly offset any processing benefit. Industry is unlikely to adopt this technology if the expenses of producing bulk ionic liquids remain at their current level (small laboratory quantities cost on the order of $1000/kg). Ionic liquids researchers and process engineers need to demonstrate that ionic liquids can be scaled up from research to industrial quantities while maintaining their chemical and thermophysical properties and purity.

Industry has been slow to focus on the application of ionic liquids and slow to recognize their potential economic value. This fact has worried the important institutions of this area. Looking for reasons and alternatives for this problem, the American Chemical Society (ACS) promoted a workshop, *Ionic Liquids: Progress and Prospects* symposium (sponsored by Green Chemistry and Engineering and Separation Science and Technology Subdivisions) at the 226th ACS National Meeting (New York, Fall 2003). The "*Barriers to Ionic Liquid Commercialization*" workshop included 36 invited participants representing 15 chemical companies, five universities, four nongovernmental organizations, and three national laboratories. A major objective of this initiative is to promote collaborative industry−academic−government R&D programs to address technical barriers. The main conclusion of this event was that chemical industry stakeholders should begin work as early as possible in areas appropriate for collaborative research. These areas include (i) process engineering user facilities, (ii) environmental, safety, and health concerns, (iii) increasing industrial focus and obtaining chemical, physical, and thermodynamic properties data, (iv) economic benefit analyses, and (v) large-scale demonstrations. Thus, specifically in the economical aspects, to accelerate ionic liquid commercialization, the investment in basic science must focus on developing predictive synthetic and property capabilities, solving important industrial and societal problems, and providing application-driven solutions not available with conventional technologies. Emphasis should be focused on developing

ionic liquids with practical industrial needs in mind: economic synthetic pathways, minimizing costs of raw materials used to make ionic liquids, extending the lifetime of the ionic liquid, minimizing toxicity, and increasing contaminant tolerability.

Today, results demonstrated in many academic papers and patents allow us to identify the main potential opportunities for ionic liquids in separations,[355–359] chemical processes,[360] polymerization reactions,[361–365] and fuel applications.[366]

One example that demonstrates that the prospective discussed here for ionic liquids is supported by results of BASF.[367] BASF has been investing in the use of ionic liquids in the industrial process and has made many advances. They have set up a research partnership with the University of Alabama (UA) to study the dissolution and processing of cellulose by means of ionic liquids. BASF sells its ionic liquids under the brand name Basionics, and the corresponding processes are marketed under the name Basil. An eco-efficiency analysis recently confirmed that the use of BASF's Basil process for scavenging acids in the chemical synthesis of phosphorus compounds offered significant advantages over the conventional system. Compared with amines, which have been used traditionally in this type of reaction, the BASF process based on 1-methylimidazole is less cost-intensive and at the same time easier on the environment. The new process for synthesizing phosphorus compounds, which are used as chemical building blocks to produce photoinitiators in UV-curable coatings, reliably avoids a number of problems encountered to date, including low stability and product yield and a laborious process.

10. Conclusions

After having examined of all the cyclocondensation reactions described in this review, it is necessary to return to the initial questions. We believe that to adequately answer the question "ILs: Solvent, Catalyst, or Both?" it is necessary to consider the characteristics of each reaction. In this review, the main effects of the ionic liquids observed in the cyclocondensation reactions were to improve the reaction yields and to shorten the reaction time. The data collected for this review showed that more than 80% of the articles reported the use of neutral reactants and neutral reaction conditions. In some cases, neutral reactants were used under Brønsted acid or basic reaction conditions, and in a few cases, Lewis acids or bases were used in the reaction media.

Although in some cases the authors emphasized ionic liquid Brønsted acid catalysis (e.g., NH or CH of imidazolium-based ILs) or Lewis acidic/basic catalysis (interaction of IL cation or anion with substrates), we believe the most important benefit of ILs in organic reactions, in particular, in condensation reactions, can be explained through the general concepts of solvent effects.

Thus, considering that most articles described in this review (i) used imidazolium-based ILs, in particular, 1,3-dialkylpyrazolium cations and nonbasic anions, (ii) used neutral reactants and neutral reaction conditions, and (iii) reported that the reactional rates were enhanced and the yields were improved in comparison to those observed in the same reaction performed in molecular solvents, we concluded that, the most important function of ionic liquid is to stabilize the charged activated complex through solvent−solute-type interactions, similar (but not identical) to the interaction between polar protic/aprotic solvents and solutes (see Figure 2).

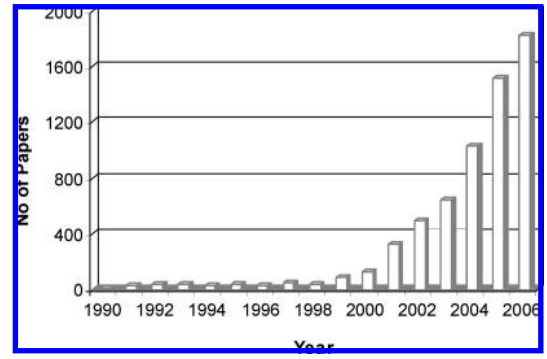


Figure 4. The rise in publications concerning ionic liquids as a function of time, as determined using Web of Science.

Moreover, considering the importance of the cyclocondensation reactions, the main reaction for heterocyclic synthesis, the information presented in this review 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.

An investigation in the Web of Science showed a proliferation of papers in the ionic liquid area (Figure 4). We found more than 7400 papers published in the period from 1990 to July 2007, 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 is surprising because the data from almost 100% of the papers reviewed here clearly show that the use of ILs in heterocyclic synthesis leads to yield enhancement and reduction in the reaction time in relation to the same reaction performed in molecular solvents. Undeniably, ionic liquids enable more efficient reactions to take place 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 review, we hope to have given a clear idea of the applicability of ionic liquids in the cyclocondensation reactions. We would like to conclude with an optimistic view for the future expansion of cyclocondensation reactions in ionic liquid media. This positive view comes from the certainty that the results reported here will be but the beginning of a great advance in this promising field in the near future.

11. List of Abbreviations

[2-AEMIM][PF_6]	1-Aminoethyl-3-methylimidazolium hexafluorophosphate
[BBIM][BF_4]	1,3-Dibutylimidazolium tetrafluoroborate
[BDMIM][Tf_2N]	1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide
[BDMIM]-[$PFBuSO_3$]	1-Butyl-2,3-dimethylimidazolium perfluorobutylsulfonate
[BMIM][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[BMIM][Br]	1-Butyl-3-methylimidazolium bromide
[BMIM][Br_3]	1-Butyl-3-methylimidazolium tribromide

[BMIM][Cl]	1-Butyl-3-methylimidazolium chloride
[BMIM][OH]	1-Butyl-3-methylimidazolium hydroxide
[BMIM][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
[BPy][BF_4]	1-Butylpyridinium tetrafluoroborate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DEAD	Diethylazodicarboxylate
DIEA	Diisopropylethylamine
DHPM	3,4-Dihydropyrimidin-2-(1*H*)-one
DMAD	Dimethylacetalenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
EDA	Ethyl diazoacetate
EDDA	Ethylenediammonium diacetate
Fmoc-Pro-Cl	9-Fluorenylmethoxycarbonyl prolyne acid chloride
[HBIM][BF_4]	1-Butyl imidazolium tetrafluoroborate
[HeMIM][BF_4]	1-Hexyl-3-methylimidazolium tetrafluoroborate
[HMIM][Tfa]	1-Methylimidazolium trifluoroacetate
HTIB	[Hydroxyl(tosyloxy)iodo]benzene
MCRs	Multicomponent reactions
[NBP][$FeCl_4$]	Butylpyridinium tetrachloroferrate
NBS	*N*-Bromosuccinimide
PEG-ILPs	Poly(ethyleneglycol)−ionic liquids
PsMim	Polystyrene−methylimidazolium
TBAB	Tetrabutylammonium bromide
TEBAC	Triethyl benzylammonium chloride
TFA	Trifluoracetic acid
Tfa	Trifluoroacetate anion
TMGT	1,1,3,3-*N*,*N*,*N*′,*N*′-Tetramethylguanidinium trifluoracetate
TMSCN	Trimethylsilylcyanide
TosMIC	*p*-Toluenesulfonyl methylisocyanide

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