SYNTHESIS OF HETEROCYCLES IN NON-CONVENTIONAL MEDIA: THE CASE OF IONIC LIQUIDS

DOI: http://dx.medra.org/10.17374/targets.2023.26.356

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Abstract. *The synthesis of heterocycles is a prominent feature of organic chemistry, due to the enormous importance of such compounds in fields like medicinal or industrial chemistry. In the effort of improving their synthesis, the nature of the solvent plays a pivotal role. In this context, the use on non-conventional solvent like ionic liquids can determine significant improvements reaction outcomes, sustainability of the process, and possibility to be coupled with non-conventional synthetic methodologies, like ultrasounds or microwave irradiation. In this chapter, we present a bird's-eye view on recent examples of the application of ionic liquids as solvents or catalysts, evidencing, whenever possible, the differences with reactions in conventional organic solvents.*

Contents

1. Introduction

The synthesis of heterocyclic compounds is a major endeavor in present-day organic chemistry, due to the prominent role exerted by these compounds in fields like medicinal and industrial chemistry. In every synthetic transformation, including the ones of heterocycles, the solvent is an almost unavoidable component, which, in many cases, exerts a crucial influence on reaction rates and outcome. The nature of the solvent is also extremely important in evaluating the sustainability of a process.[1] Based on these considerations, it is reasonable to expect that switching from classical organic solvents to non-conventional organic solvents like ionic liquids (ILs) can induce significant changes in reactivity and reaction outcomes.

Ionic liquids are organic salts with a low melting point, conventionally lower than 100 °C,[2, 3] and many of them are liquid at room temperature and can be used as solvent. Structure of typical cations and anions encountered in ILs are reported in Table 1.

Being composed exclusively by ions, ILs display a completely different set of properties compared with organic solvents.[4,5] First of all, ILs have generally negligible vapour pressure and flammability, and consequently ILs were initially considered more environmentally friendly alternatives to conventional organic solvents. A strong point of ILs is the fact that their properties can be varied to a large extent and in a straightforward way by changing their anions.

A distinct feature of ILs is their high degree of structural organization.[6,7] Indeed, thanks to the interplay of non-covalent interactions like hydrogen bonding, van der Waals and coulombic interactions as well as π-π in ILs with aromatic ions, ILs nanostructure persists in the liquid state and to a certain extent, even in the gas phase.[8] For these reasons, ILs can be considered as supramolecular fluids.[9] When used as solvents or reaction media, ILs provide a solvation environment that is completely different from the ones of conventional solvents. Moreover, many ILs are immiscible with organic solvents and therefore they can potentially be recycled. One of the most important effects of ILs on organic reactivity comes from the effect of their structural organization.[10] Indeed organized fluids like ILs can be considered "entropic drivers"[11] and such effects operate, in many cases, by changing the activation parameters,[12-14] as demonstrated also in studies conducted

on transformation of heterocycles.[15] In such case, bulk polarity parameters, such as the Kamlet-Taft ones,[16] fail to explain the reactivity observed.

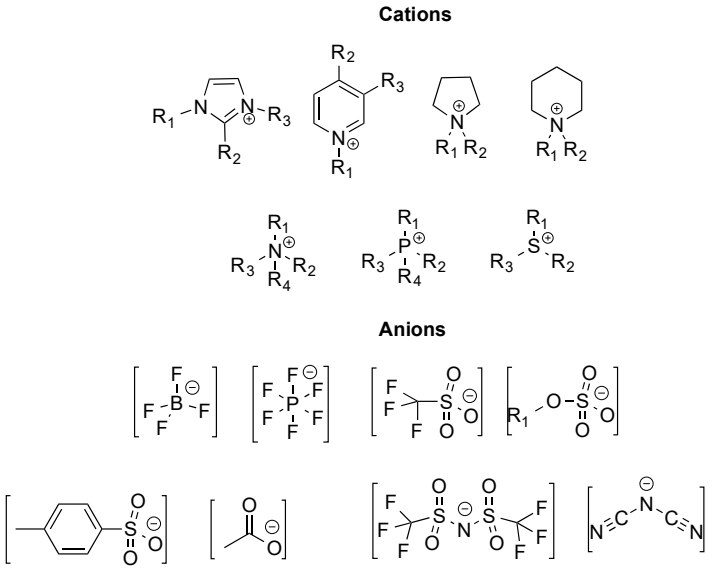


Table 1. Structures of cations and anions frequently encountered in ILs.

Another way in which ILs can determine significant variation in reactivities is by radically changing the basicity and acidity of acid[17] and base catalysts,[18,19] compared with the one in molecular solvents. ILs can also be suitably functionalized with reactive groups to exert a catalytic function. Such ILs are commonly known as Task Specific Ionic Liquids (TSILs)[20] and can exert the dual role of solvents and catalysts.

In this chapter, we present a bird's eye view on recent literature describing the use of ILs as solvents and/or catalysts for heterocyclic synthesis. Whenever possible, we highlight the difference in reactivity or reaction outcome arising from the use of ILs instead of conventional solvents.

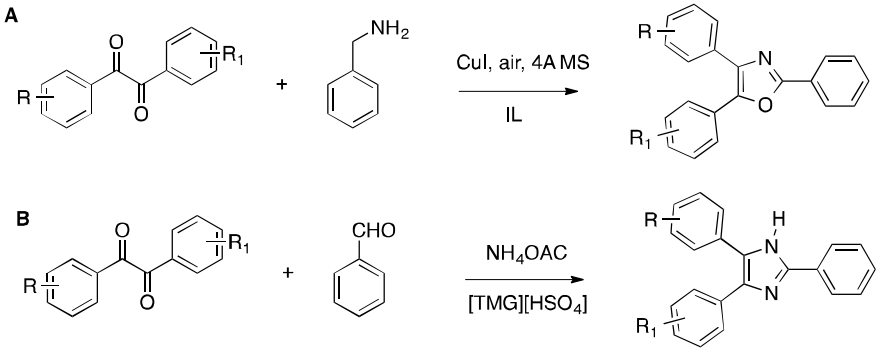
The chapter sections are ordered on increasing complexity of the heterocyclic structures synthesized. First, the synthesis of simpler 5- and 6- membered heterocycles is presented. In the next section, we discuss works dealing with the synthesis of benzofused and bicyclic heterocycles. The final section includes works describing the use of ILs in the synthesis of more complex heterocyclic scaffolds, such as polycyclic and spirocyclic compounds.

2. Synthesis of 5- and 6-membered heterocycles

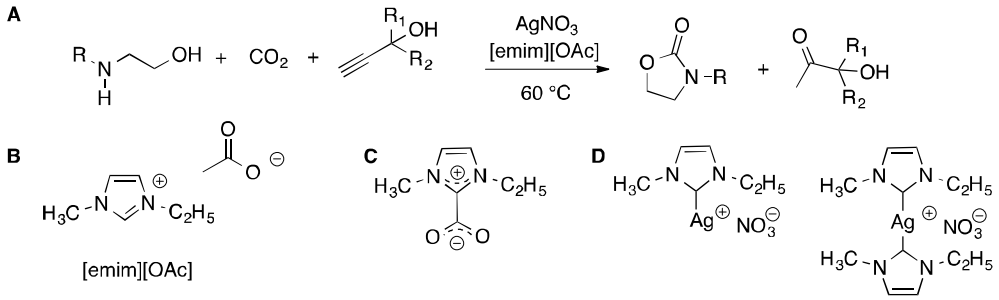
Regarding the synthesis of 5-membered heterocycles, Laali and coworkers reported on the preparation of a library of 2,4,5-triaryloxazoles and 2,4,5-triarylimidazoles from 1,2-diaryldikenones, in imidazolium- and guanidinium-based ILs, respectively. (Scheme 1).[21] In particular, the synthesis of 2,4,5-triaryloxazoles, involving the oxidative coupling of the diketones with benzylamines was carried out at room temperature for at most two hours, obtaining yields higher than 80%. A mechanism was hypothesized, involving initial oxidation of the Cu(I) center to Cu(II) and subsequent coordination by the amino group, although with no particular role of the IL. Similar results were obtained for the synthesis of 2,4,5-triarylimidazoles, in which case the obtainment of yields higher than 80%, required much longer times, in the range 20-24h. For both reactions, the ILs could be reused three times with no substantial decrease of the yield.

Fixation of atmospheric CO_2 can be conveniently exploited for the synthesis of heterocycles. In this regard, Verpoort and co-workers described the atom-economy synthesis of 2-oxazolidinones and α-hydroxyketones by reacting 2-amino alcohols, propargyl alcohols and CO_2 in the presence of $AgNO_3$ in the IL [emim][OAc] (Scheme 2A-B).[22] The reaction proceeded with excellent yields in most cases, requiring only

a loading in metal salt equal to 0.25%, which is lower than many currently reported procedures for the same reaction. Notably, the IL could be recycled 5 times with no loss in yield. The authors carried out a thorough analysis of the green metrics of the reaction, considering parameters like E-factor, Reaction Mass Efficiency (RME), mass intensity (MI) and mass productivity (MP), showing that this protocol is superior in terms of sustainability to the methods currently reported for the same transformation. Finally, a detailed mechanistic investigation revealed that the presence of the basic carboxylate anion is essential to obtain high yields and that the imidazolium ion participates in the reaction, as testified by the involvement of N-heterocyclic carbene (NHC)-CO_2 complexes (Scheme 2C) as well as Ag-NHC complexes such as the ones depicted in Scheme 2D.



Scheme 1. Synthesis of A) 2,4,5-triaryloxazoles and B) 2,4,5-triarylimidazoles from 1,2-diaryldiketones.



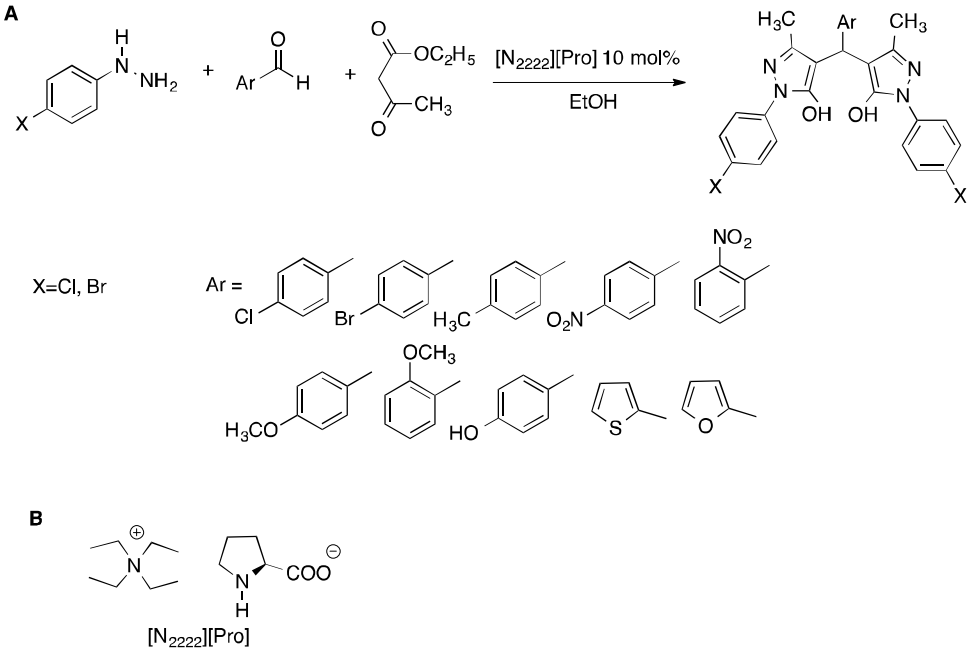
Scheme 2. A) Synthesis of 2-oxazolidinones, B) IL used, C) NHC-CO_2 adducts and D) NHC-Ag complexes.

In another example of IL-based catalyst for the synthesis of heterocyles, an ammonium prolinate salt, [N_{2222}][Pro], was successfully employed for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (Scheme 3).[23] The reaction showed a wide scope, with yields in the range of 78%-85% under optimized conditions. The IL was recycled for five runs without loss in yield. The reactions could also be performed at the gram scale with no detrimental effects on the yield. The catalytic efficiency of the prolinate IL was ascribed to its ability to act both as Lewis base and hydrogen bond donor.

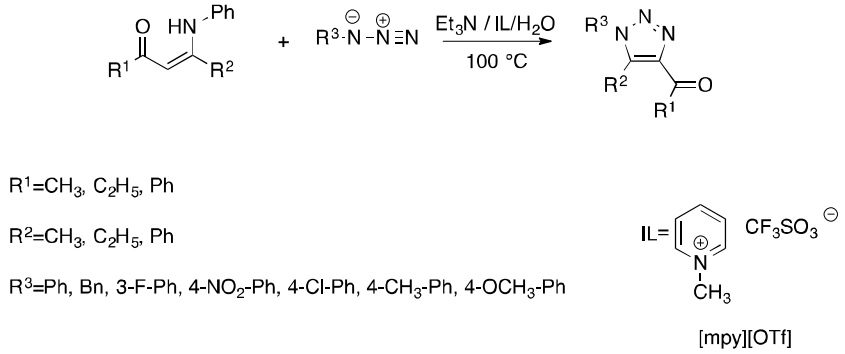
Dipolar cycloadditions between enaminones and aryl azides in a pyridinium-based IL allowed obtaining 1,4,5-trisubstituted-1,2,3-triazoles with complete regioselectivity (Scheme 4).[24] Under the optimized conditions, the triazole were obtained in yield higher than 80%, while, in the absence of IL and in conventional organic solvents, no reaction occurred. In all cases, the reaction took place with complete regioselectivity, yielding the regioisomer with the electron-deficient group of the enaminone in position 4 and the alkyl substituent in position 5 as the only product. A mechanistic investigation, supported by DFT-calculations, suggested that the reaction proceeds *via* a Huisgen's concerted asynchronous 1,3-dipolar cycloaddition, followed by a favored retro-aza-Michael reaction.

A related reaction, the Cu(I)-catalysed azide-alkyne cycloaddition (CuAAc) between 4-chloroquinoline and phenylacetylene, was carried out in solution of ILs differing for the cation and anion structure (Scheme

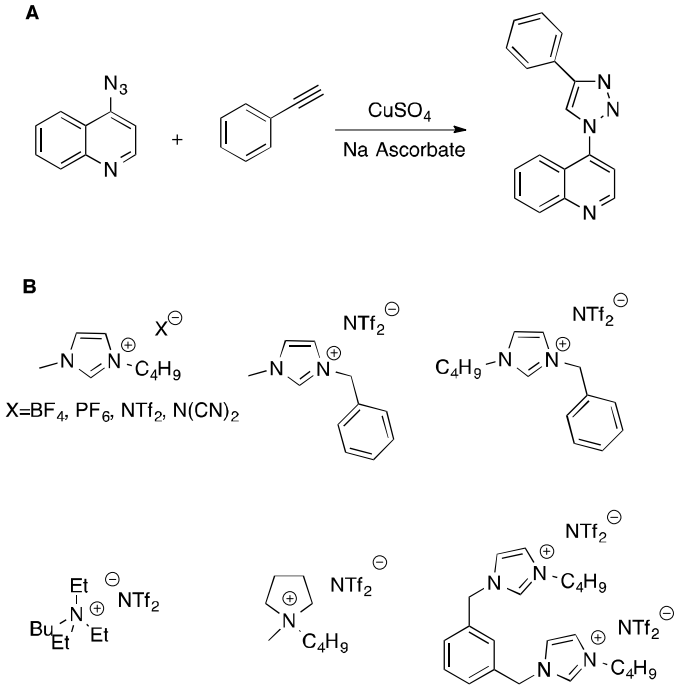
5). This reaction was performed both under conventional heating and sonochemical activation.[25] In general, in ILs as solvents, only one of the possible two regioisomeric triazoles was obtained. Under silent conditions, the trend of yields, in ILs differing for the cation, closely followed the one of structural organization as probed by Resonance Light Scattering Measurements (RLS). On the other hand, the effect of the anion was more articulated and ascribed to the concomitant effect of the hydrogen bonding accepting ability, as expressed by the Kamlet-Taft parameter β, and the IL viscosity. When the reaction was carried out under sonochemical activation, in most cases higher yields in shorter reaction times were observed, compared with the ones obtained under silent conditions. Finally, the solvent could be recycled 3 times, without significant losses in yield.



Scheme 3. A) Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s and B) IL-based catalyst.

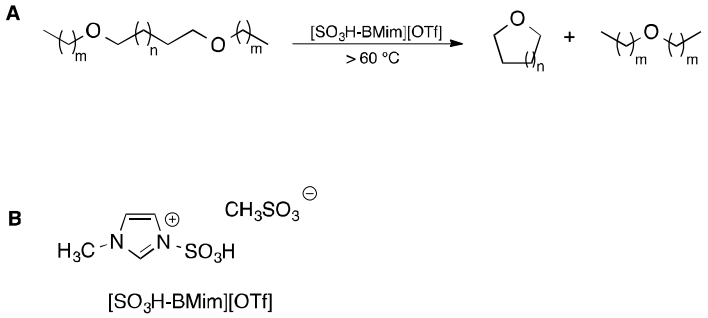


Scheme 4. Reaction between enaminones and aryl azides, substrates and IL used.



Scheme 5. A) CuAAC between 4-chloroquinoline and phenylacetylene and B) ILs used as solvents.

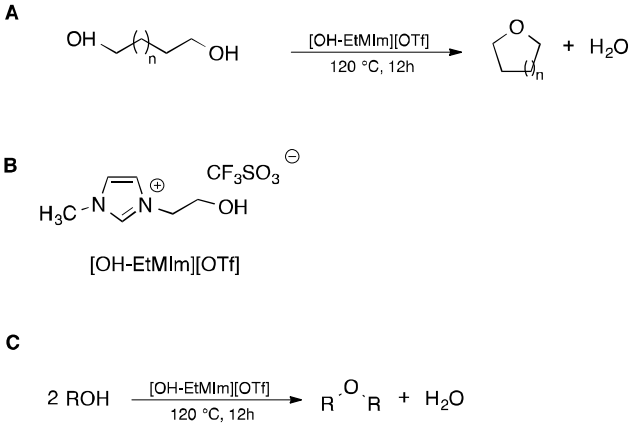
Ring closing metathesis of polyethers is an effective route for the synthesis of oxygenated heterocycles like tetrahydrofurans, tetrahydropyrans and morpholines. Typically, these reactions require the presence of a metal-based Lewis acidic catalyst, like salts of Fe(III), Sc(III) or Al(III). The use of an imidazolium-based IL functionalized with a sulfonic acid group allowed the reaction to be carried out under solventless conditions, in a biphasic reaction system, without the need for metal salts.[26] The reaction and the structure of the IL catalyst are reported in Scheme 6.



Scheme 6. A) Ring-closing metathesis reaction and B) acidic IL catalyst.

Under optimized conditions, 5- and 6-membered *O*-heterocycles such as phenyl-substituted tetrahydropyranes and tetrahydrofuranes, as well as tosyl- and nosyl-protected morpholines, could be synthesized in excellent yields. The reactions could also be conducted at the gram scale with no significant reduction in yield. Notably, the acidic IL catalyst was also effective in promoting ring-closing metathesis of ethers which could not be transformed in the presence of Lewis-acidic metal salts. Mechanistic investigation

pointed out the crucial role of hydrogen bonding involving IL cation and anion with the substrates, for the reaction to occur. The same group used this strategy to carry out the dehydrative cyclization of glycols in the presence of an hydroxylated imidazolium IL devoid of acidic functionality and bearing an hydroxyl group on the cation, [OH-EtMim][OTf] (Scheme 7A-B).[27] The presence of the hydroxyl moiety on the cation enhanced its hydrogen bond donating ability, and the excellent yield and selectivities observed, confirmed the crucial role of hydrogen bonding in catalyzing such process. On the other hand, the absence of a strongly acidic group on the IL rules out that acid catalysis is the main reaction pathway. Notably, the reactions were carried out at 120 °C, which is a relatively mild condition for this process. Chirality transfer experiments, performed by using enantiopure chiral diols, revealed almost total inversion of configuration in the products, strongly suggesting the occurrence of S_N2 pathway. Notably, the protocol could be extended to the etherification of alcohol, obtaining excellent yields also in this case (Scheme 7C). Evidence for strong hydrogen bonding involving the IL and the substrate was found by *in situ* ^{1}H NMR analysis and attenuated total reflection infrared spectroscopy (ATR-FTIR). Moreover, high-resolution electrospray ionization mass spectrometry analysis showed the occurrence of species like $[(HO\text{-}EtMim)(CH_3OH)_2^+]$, once again hinting at strong interaction between the IL and the alcohol substrates. Finally, DFT calculations pointed out that also the anion of the IL is involved in the activation of the substrate by hydrogen bonding.

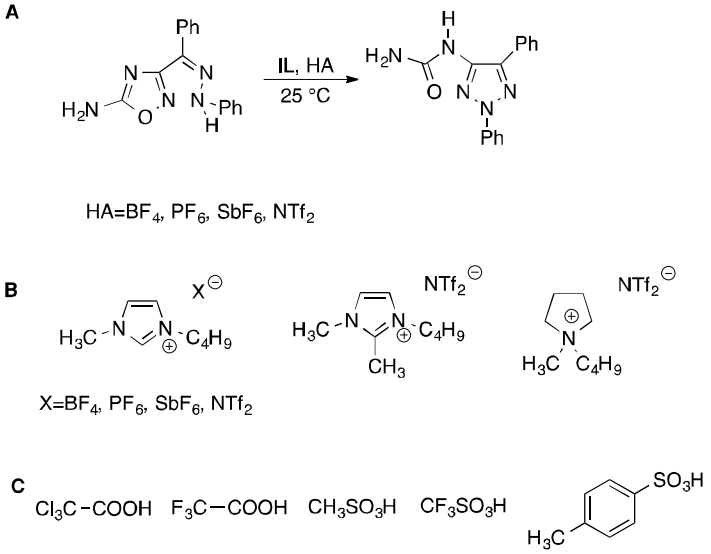


Scheme 7. A) Dehydrative cyclization of glycols, B) hydroxylated IL catalyst and C) dehydration of alcohols.

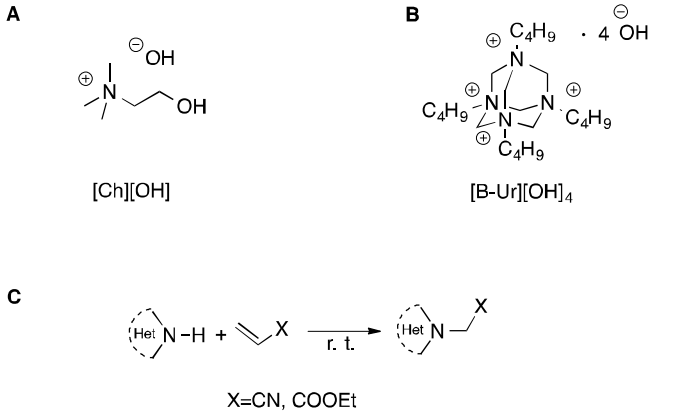
The acid-catalyzed heterocyclic rearrangement of the *Z*-phenylhydrazone of the 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant 1,2,3-triazole was studied in ILs differing for the cation and anion, in the presence of sulfonic and carboxylic acids as catalysts (Scheme 8).[28] Kinetic experiments pointed out the that reaction rate was higher in ILs than in conventional solvents like methanol and 1,4-dioxane, ascribed to weaker solvation interaction operating in ILs. The strength of sulfonic acids was measured in each IL, finding that all acids were stronger in solution of IL compared with conventional solvents. Moreover, within ILs, the acidic strength of each catalyst was mainly affected by the IL anion. Overall, the results obtained revealed that the trend of second-order rate constants in IL differing for the anion, largely depended on the difference of acidic strengths of the catalysts. On the other hand, variation of the IL cation gave a more articulate trend, explained as a balance of acidic strength and stabilization of substrate and transition state by π-π interaction with the aromatic IL cations.

A protocol for the functionalization of aromatic and aliphatic nitrogen-containing heterocycles through aza-Michael reaction was described, employing the use of basic ILs like cholinium hydroxide [Ch][OH] and *n*-butyl-urotropinium hydroxide $[B\text{-}Ur][OH]_4$, as depicted in Scheme 9.[29] Under the optimized condition, the reaction could be carried out at room temperature in the presence of both catalysts, and led from good to excellent yields (70%-96%) of products from a diverse range of substrates (comprising imidazole, alkylimidazoles, indole and morpholine). It is worth noting that, in the case of [Ch][OH], water is present in

the reaction mixture as a co-solvent, whereas in the case of [B-Ur][OH]$_4$ the process occurs under neat conditions. Finally, [B-Ur][OH]$_4$ could be used 5 times without reduction in yield, performing the reaction at the gram scale.

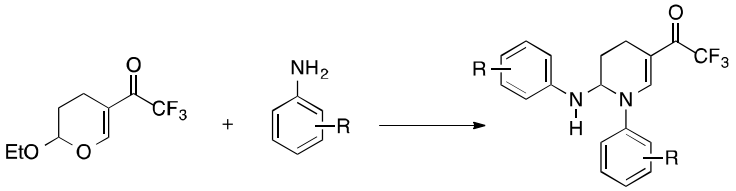


Scheme 8. A) Heterocyclic rearrangement reaction, B) ILs used as solvents and C) acid catalysts.



Scheme 9. A) Cholinium hydroxide, B) *n*-butyl-urotropinium hydroxide and C) aza-Michael reaction.

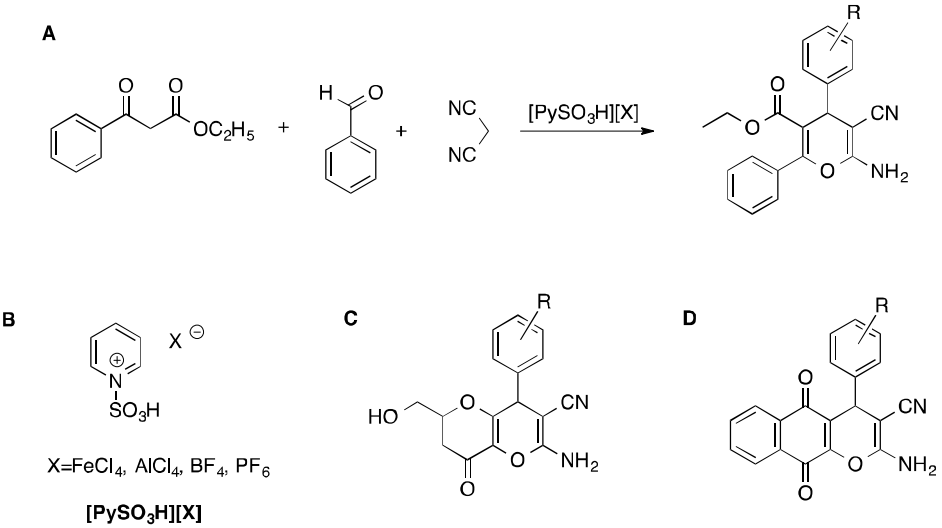
Zanatta and co-workers described the synthesis of a series of 1-aryl-2-arylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridine derivatives in [bmim][BF$_4$] as solvent, also under microwave irradiation (Scheme 10).[30] Replacing conventional solvents with the IL [bmim][BF$_4$] enabled the reaction to be performed at a room temperature as opposed to reflux conditions, and allowed obtaining significantly higher yields after 1 h as compared with the 24 h required in ethanol. Furthermore, for seven of the substrates considered, the reaction took place only when the IL was employed as solvent. Finally, the reaction was also carried out under microwave irradiation, obtaining yields comparable to the ones obtained in conventional heating conditions, but after only 1 min of irradiation, suggesting a synergistic effect between IL and microwave irradiation.



R=H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-Cl, 3-Cl, 4-Cl, 2-F, 3-F, 4-F, 4-Br

Scheme 10. Synthesis of 1-aryl-2-arylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridine derivatives.

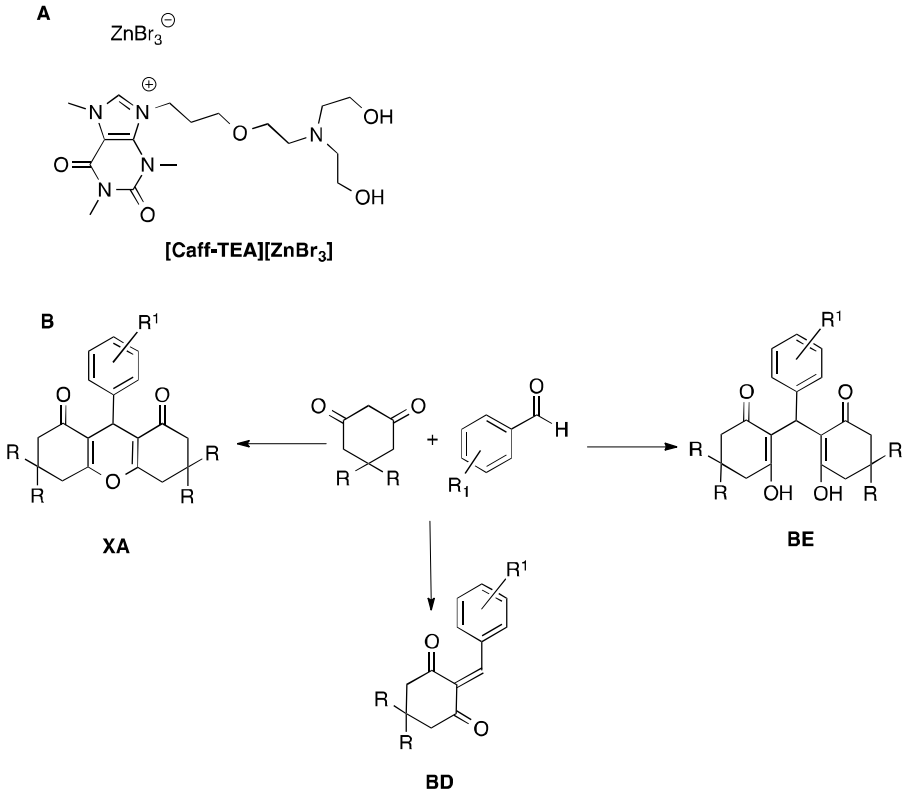
A series of 2-amino-4*H*-pyranes was obtained by a three-component reaction involving malononitrile, arylaldehydes and β-ketoesters and promoted by acid-functionalized pyridinium ILs (Scheme 11A-B).[31] In general, good to excellent yields were obtained in the presence of all ILs, and the catalyst could be recycled up to four times with marginal decline in yield. The reaction protocol could also be extended to the synthesis of 2-amino-4,8-dihydropyranes and 2-amino-4*H*-chromenes (Scheme 11C-D).



Scheme 11. A) Synthesis of 2-amino-4*H*-pyranes, B) Pyridinium-based IL catalyst, C) 2-amino-4,8-dihydropyranes D) 2-amino-4H-chromenes.

Heterocyclic building blocks play a pivotal role in the synthesis of complex chemical compounds and biological molecules. This is the reason why during the years a great deal of attention has been devoted to the identification of synthetic strategies also able to comply with the full respect of environment. In this regard, the use of eco-friendly task specific ionic liquids (TSILs) can offer the dual advantage of achieving high yields and conversions, under mild reaction conditions. Among the interesting heterocyclic nuclei benzylidenes, bis-hydroxyenones and xanthenes can be included.

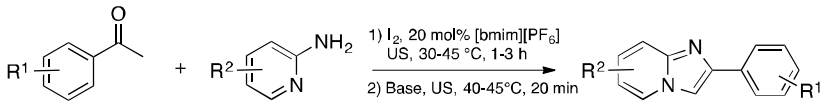
In particular, their synthesis was accomplished using a natural-based TSIL, like caffeine-triethanolamine zinc tribromide [caff-TEA][$ZnBr_3$], and the product obtained depended on the stoichiometry of the reagents (Scheme 12).[32] The IL was used both as solvent and catalyst, under ultrasound irradiation. Optimization of experimental conditions demonstrated that the above solvent-catalyst allowed achieving yields ranging from 79% to 95%, operating at 80 °C with reaction times ranging from 15 up to 40 min. The results obtained proved better than the ones previously reported in the literature. The good performance of this TSIL was understood by ^{1}H NMR analysis of the intermediates, demonstrating the activation of the carbonyl portions of aldehyde and dimedone by the IL, which drove up the whole process.



Scheme 12. A) Structure of the caffeine-based TSIL and B) schematic representation of the synthesis of benzylidenes (BD), bis-hydroxyenones (BE) and xanthenes (XA).

3. Synthesis of benzofused and bicyclic heterocylcles

The synthetic importance of fused heterocyclic compounds derives from the recurring involvement of these nuclei in many pharmaceutically active compounds. The synthesis of imidazo[1,2-a]pyridines was carried out under neat conditions, using [bmim][PF_6] as catalyst. The reactions were performed under sonchemical activations, and for comparison, under conventional heating (Scheme 13).[33] The reactions gave good to high yields, in the range 58%-86%, with a reasonable wide substrate scope. Ultrasonic activation allowed the process to occur with much higher yields compared with silent conditions, at lower temperatures (30-45 °C under sonochemical conditions as opposed to 110 °C under silent conditions) and in shorter times (20 minutes with ultrasounds and 1 hour under conventional heating).

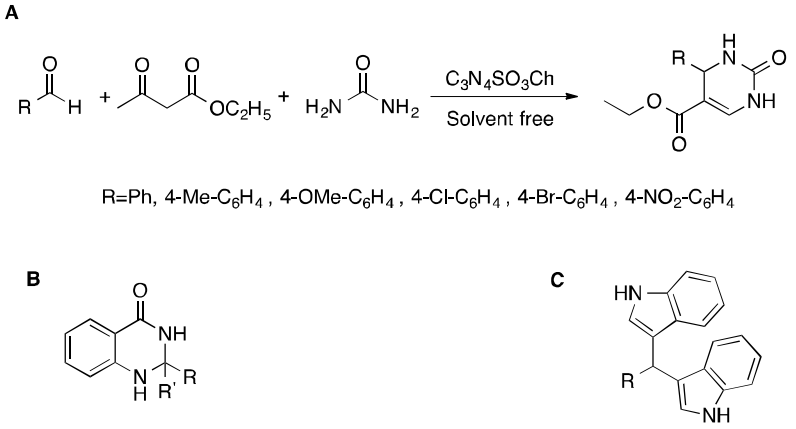


R^1=H, 4-Br, 4-OMe, 4-NO_2, 3-NO_2, 2-OH, 4-SO_2Me

R^2=H, 4-Me

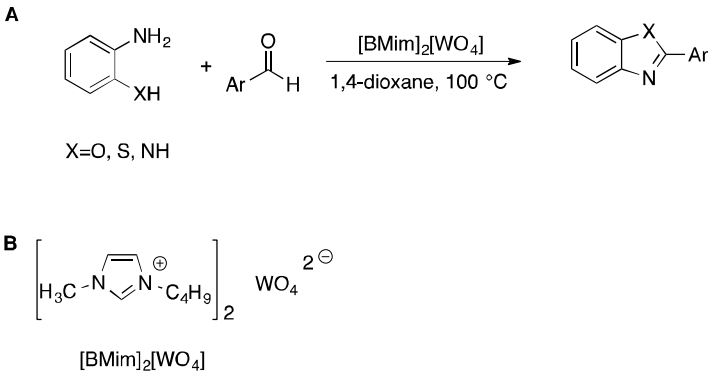
Scheme 13. Synthesis of imidazo[1,2-a]pyridines.

In a different example, a cholinium-based IL was supported on acid-functionalized porous carbon nitride sheet and used as heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones by Biginelli reaction (Scheme 14).[34] In particular, the carbon nitride support was first prepared by heating melamine at 550 °C, then sonicating the resulting material in dichloromethane in the presence of chlorosulfonic acid to introduce $-SO_3H$-functionalities. Finally, treatment at room temperature with cholinium hydroxide afforded the catalyst used. The introduction of the cholinium salt resulted in significant improvement of the surface area of the catalyst. Good to excellent yields were obtained (76%-94%) and the catalyst could be reused 5 times with no reduction in yield. This catalyst also proved versatile, since it was effective also in promoting the synthesis of bis-indolyl-methanes and 2,3-dihydroquinazolines through the same approach (Scheme 14B-C).



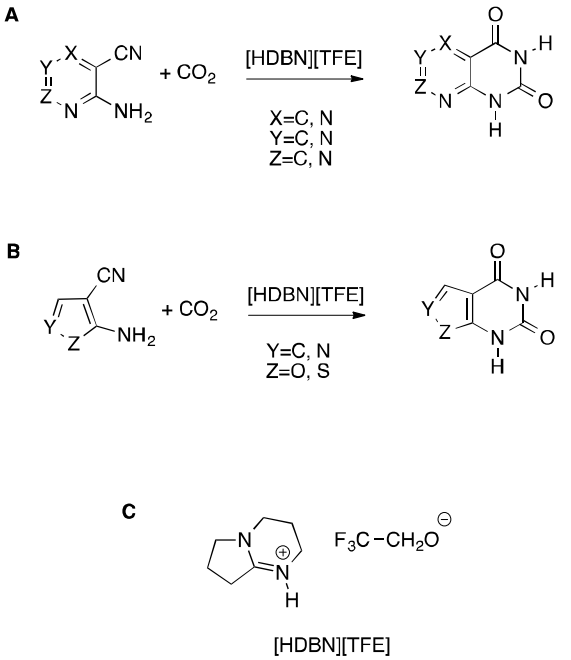
Scheme 14. Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones promoted by carbon-nitride supported IL.4.

An imidazolium IL bearing a metal-based anion was successfully employed for the synthesis of different heterocycles like benzoxazoles, benzothiazole and benzimidazoles.[35] In particular, the reaction was promoted by the tungstate IL $[BMIm]_2[WO_4]$, as reported in Scheme 15. The target heterocycles were obtained with good to high yields, although it is worth noting that the solvent used is not an IL but 1,4-dioxane. Temperature-dependent ^1H and ^{13}C NMR measurements suggested that the IL is actually a pre-catalyst and that, under the experimental conditions used, the tungstate deprotonates the imidazolium cation, forming the relevant carbene, which is the actual catalyst.



Scheme 15. Synthesis nitrogen-containing heterocycles and B) tungstate-based IL catalyst.

As previously mentioned, fixation of CO_2 can be used successfully for the IL-promoted synthesis of heterocycles. In a related example, CO_2 at atmospheric pressure allowed the obtainment of heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-diones, from 5-and 6-membered nitrogen-containing heterocyclic compounds, in a process catalysed by the IL [HDBN][TFE], which also plays the role of solvent (Scheme 16).[36] In the absence of IL, no reaction took place. In general, moderate to excellent yield (52%-95%) were obtained using 6-membered heterocycles as starting materials, while in the case of 5-membered heterocyclic substrate, yields were comprised in the range 65%-94%.

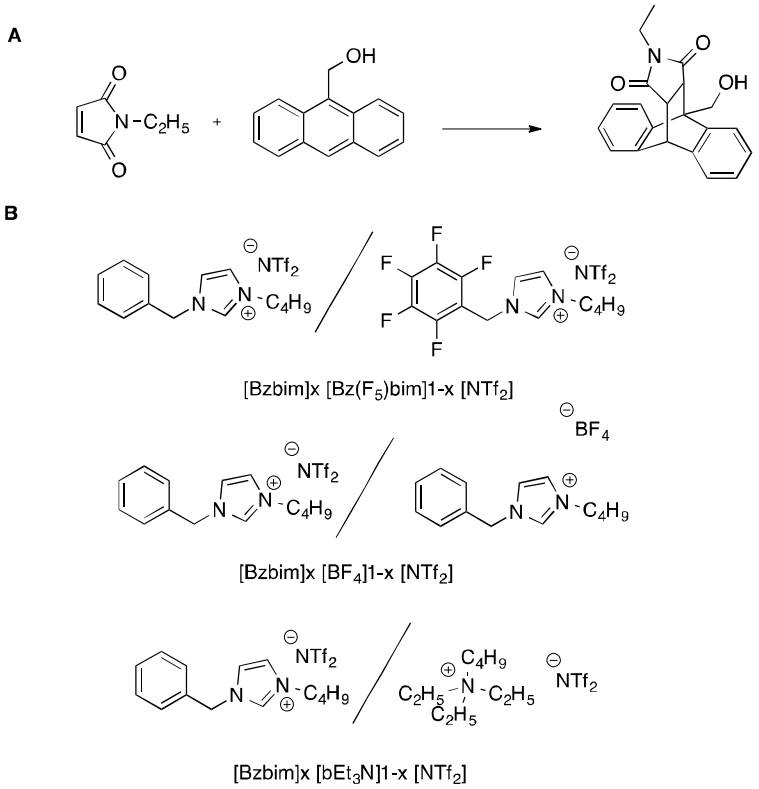


Scheme 16. Synthesis of heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-diones fromA) 5-memebered heterocycles, B) 6-membered heterocycles. C) IL used as catalysts and solvent.

The Diels-Alder reaction between 9-anthracenemethanol and *N*-ethylmaleimide was used as probe reaction to study the structural organization of mixtures of ILs.[37] In particular, the reaction was carried out in mixtures of ILs differing for both the cation and anion, spanning the whole compositional range (Scheme 17). The rate of reaction was determined as a function of the mixture composition, while the structural organization of the IL mixture was investigated by means of ^{1}H NMR measurements, Resonance Light Scattering, and UV-vis spectra of the solvatochromic probe Nile Red. Kinetic investigations revealed a non-monotonic trend of the observed kinetic constant as a function of the mixtures composition. In general, the reactivity could be rationalized in terms of the concomitant effect of solvent organization and viscosity. In particular, the largest reactivity variations were observed in the mixture composed by ILs differing for the anions, where reactivity trend closely follow the variation in structural organization as probed by RLS and ^{1}H NMR investigations. On the other hand, in mixtures differing for the cation, smaller variations in the structural order degree were found as a function of composition, and viscosity effects became also important. The whole of results showed that these mixtures behaved as IL double salts.

In another example, changing the IL cation and anion greatly affected the selectivity in the cycloisomerizations of 2-alkynyl-benzoic acids, which afforded as only products isobenzofuranones or 1*H*-isochromen-1-ones depending on the IL used and the substitution pattern on the triple bond of the substrates (Scheme 18).[38] In particular, the isobenzofuranone product was obtained in the presence of substrates bearing aromatic groups on the triple bond and in solution of the aliphatic IL $[Mor_{1,2}][N(CN)_2]$,

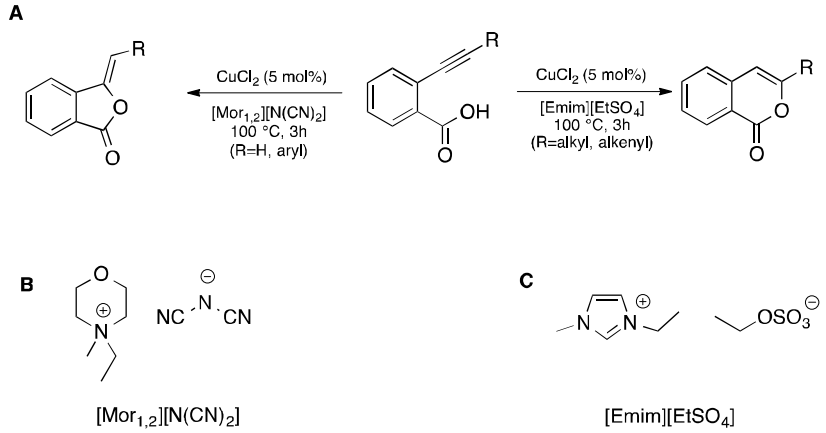
reported in Scheme 18B. On the other hand, the 1*H*-isochromen-1-ones were the only products observed from substrates bearing alkyl or alkenyl on the triple bond, using the imidazolium-based IL [Emim][$EtSO_4$] (Scheme 18C). Using other ILs as solvents, mixtures of these products were obtained. DFT-calculations revealed that the two products arose from two distinct mechanistic pathways, and also that the IL anion could affect the reaction outcome by coordinating the metal center, or acting as a base, facilitating the deprotonation of the carboxylic moiety. In all cases, good to high yields were obtained, and the solvents could be used for five consecutive runs, with no loss in yield.



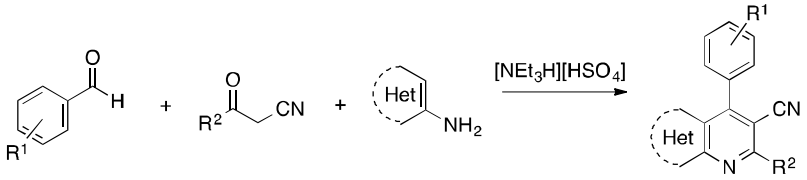
Scheme 17. A) Diels Alder reaction and B) IL mixtures considered.

In another example of one-pot multicomponent reaction, Gill and co-workers described the synthesis of pyrido[2,3-d]pyrimidine and pyrazolo[3,4-b]pyridine hybrids,[39] catalysed by the acidic IL [Et_3NH][HSO_4], as depicted in Scheme 19. In particular, the reactions were carried out under solventless conditions, and a library of 39 compounds could be prepared, with excellent yields. Furthermore, the reaction could be performed at the gram scale maintaining high yields and the IL could be recycled 5 times with no significant reductions in yield.

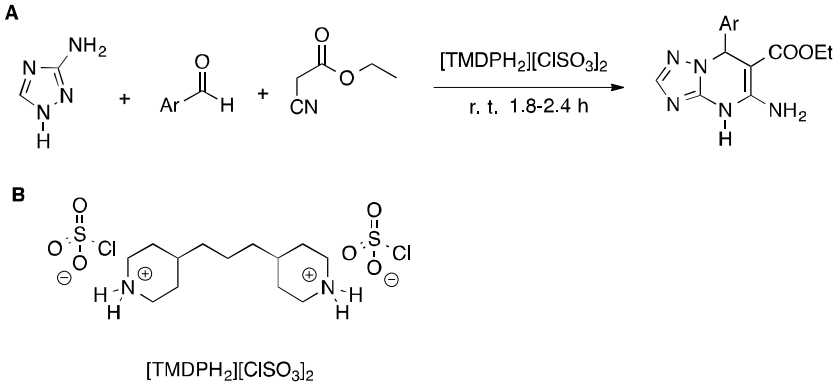
Similar considerations were also true also for dicationic ILs like 4,4′-trimethylene-*N*,*N*′-dipiperidinium chlorosulfonate [$TMDPH_2$][$ClSO_3$]$_2$, which successfully promoted the one-pot reaction synthesis of triazolo[1,5-a]pyrimidine scaffolds, playing the dual role of solvent and catalyst. (Scheme 20).[40] The results obtained showed that the highest yields were obtained conducting the reaction in pure IL, whereas the presence of co-solvents led to the obtainments of lower yields. The scope of the reaction was explored by changing the nature of the aldehyde, finding yields in the range of 73-94%. In particular, highest yields and fastest rates were observed for aldehydes bearing electron-withdrawing substituents. The reaction could be performed at the gram scale, without significant loss in yields, and the IL could be reused for five consecutive runs.



Scheme 18. A) Cycloisomerization reaction B) aliphatic IL and C) aromatic IL solvent considered.



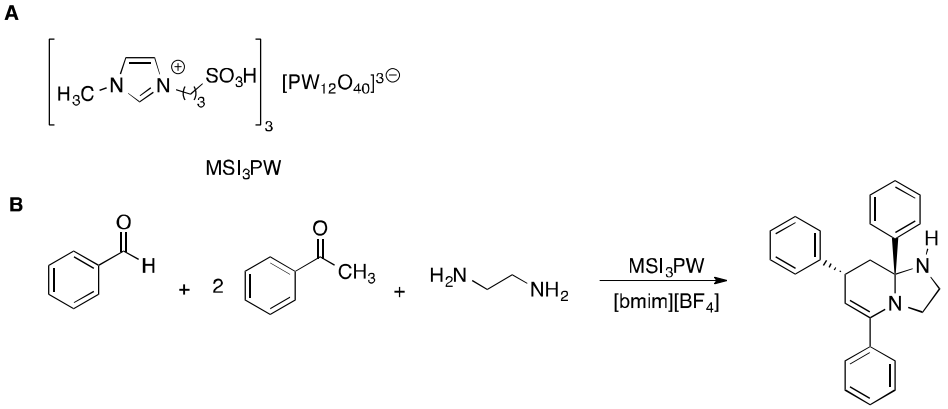
Scheme 19. A) Synthesis of fused pyridine derivatives.



Scheme 20. A) One-pot synthesis of dihydro-6*H*-chromeno[4,3-b]isoxazolo[4,5-e]pyridines and B) IL catalyst.

In another example of multicomponent reaction, a remarkable regioselectivity was obtained using an acidic IL as catalyst, in the one-pot synthesis of hexahydroimidazo[1,2-α]pyridine derivatives, through a pseudo four-component reaction. In particular, the IL catalyst used, MSI_3PW, bore a sulfonic acid functionality in the cation, and the anion was a heteropolyacid (Scheme 21A).[41] The model reaction involved benzaldehyde, acetophenone and ethylenediamine, while the IL [bmim][BF_4] was used as solvent, as reported in Scheme 21B. The reaction was carried out at 70 °C in [bmim][BF_4] and in several conventional solvents spanning a wide polarity range, including both protic and aprotic solvents. In general, the yield obtained in IL was much higher than the ones observed in conventional solvents, with the sole exception of methanol. However, attaining a yield of 90% in the IL required 1h, whereas in methanol, the same yield was obtained only after 12

h. Notably, the only product formed was the *trans*-isomer, as ascertained by ^{1}H NMR and X-ray crystallographic analysis. Then, the scope of the reaction was explored, finding that changing the structures of the aldehyde and ketones afforded good to excellent yields, still maintaining the same regioselectivity described above. A detailed mechanistic investigation was performed, by ESI-MS. To this aim, the authors prepared analogs of the reagents functionalized with cationic groups acting as tags, to facilitate the detection of intermediates by ESI-MS. The results obtained suggest the occurrence of two parallel mechanistic pathways, both converging to the same product. Under both hypotheses, the first step of the reaction involved protonation of the ketones by the acidic IL catalyst, forming an intermediate imine.



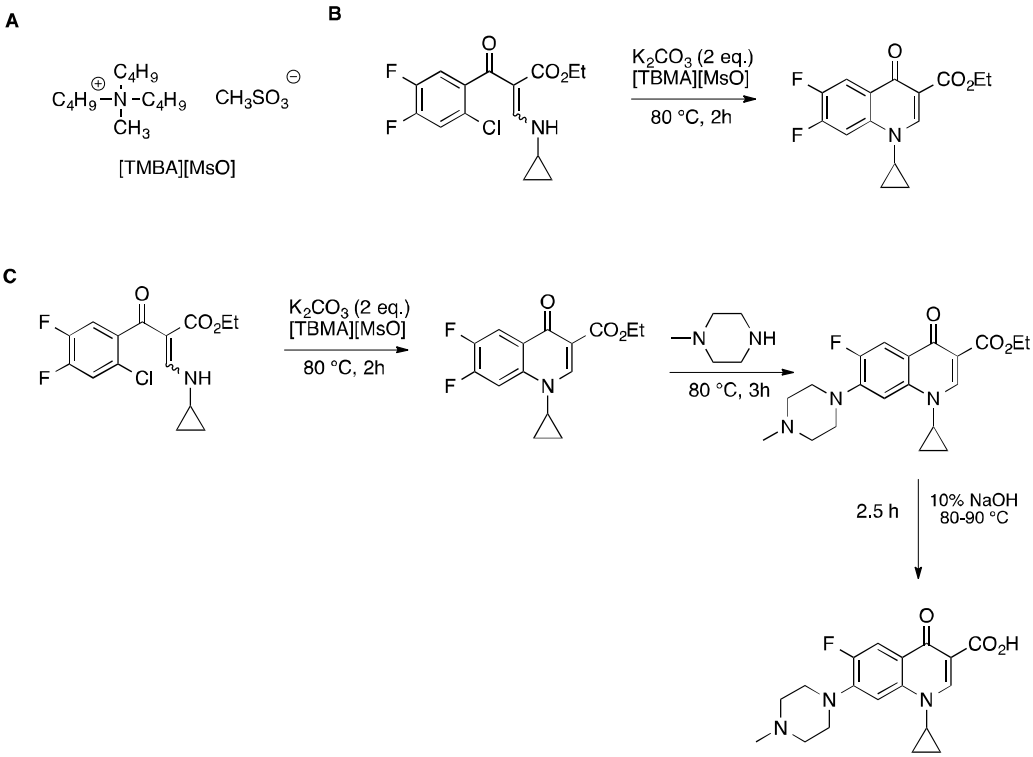
Scheme 21. A) Heteropolyacid containing IL catalyst and B) pseudo four-component reaction.

A similarly relevant heterocyclic nucleus in the pharmaceutical fields is 4-quinolone, which, for example, is present in the antibiotic drug ciprofloxacin. In this regard, Manfroni and co-workers described the synthesis of 4-quinolones by cyclization of benzoylacrylates, using the ammonium-based IL [TBMA][MsO] as solvent and potassium carbonate as catalyst (Scheme 22A-B).[42] Using this IL allowed DMF to be replaced as the solvent for such process. In particular, under the optimized conditions, the yield obtained in solution of [TBMA][MsO] was higher than the one in DMF, 78% and 65%, respectively. The IL could also be recycled for three times, with only a small reduction in yield after the third reuse. Furthermore, the reaction showed a wide scope, maintaining yields higher than 70%, by varying the structures of either the aromatic ring or the group attached to the nitrogen in the side chain. Finally, the IL allowed to carry out the full Grohe cycloaracylation process, a classical synthetic route for the synthesis of fluoroquinolone-based antibiotics, in a one-pot, three-step fashion (Scheme 22C). In particular, the product synthesized was the fluoroquinolone known as UB-8902, recently explored against the multi-resistant bacterial strain *Acinetobacter Baumanii*.[43] A remarkable overall yield of 65% was obtained, without the need of isolating the intermediates.

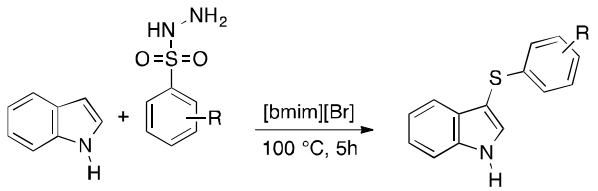
The use of ILs in heterocyclic chemistry is important not only in the direct synthesis of heterocyclic nuclei, but also for their functionalization. In this context, the functionalization of indole to form unsymmetrical diaryl sulfides was carried out in the presence of sulfonylhydrazides as source of sulfur, in [bmim][Br] as solvent (Scheme 23).[44] Under optimized conditions (100 °C for 5 h) yields in the range 65%-82% were obtained. However, the scope investigated was limited to four sulfonylhydrazides and attempts to recycle the IL showed a regular decline of yield at each reuse, over five total runs. For this reaction, the use of IL resulted in improved regioselectivity compared with the same process carried out in ethanol. In particular, in ethanol, sulfur introduction occurs at both positions C-2 and C-3 of indole, while in the IL only the 3-substituted product is observed.

The use of IL as solvent was beneficial in an oxidative cyclization reaction of isatoic anhydrides with arylmethylamines, promoted by iodine, for the synthesis of 2,3-disubstituted quinazolinones (Scheme 24).[45] Such heterocyclic compounds are important for the presence of the 2,3-disubstituted quinazolinones moiety in several marketed drugs. A general advantage of this protocol is that no separate precursors are required to introduce the substituents at the C-2 and N-3 positions in the final 2,3-disubstituted quinazolinone scaffold.

Using [bmim][BF_4] as solvent allowed the products to be obtained in higher yields compared with conventional solvents and in shorter reaction time. In general, good yields 67%-80% were obtained, with a good scope. Under the optimized conditions, the reaction could be carried out at the gram scale, maintaining good yields, and the IL could be reused successfully over four cycles. Radical quenching experiments ruled out the occurrence of a radical-mediated pathway, while conducting the reaction under anaerobic conditions, confirmed the role of I_2 as the sole oxidant.



Scheme 22. A) IL used as solvent, B) model cyclization reaction and C) synthesis of 3-carboxyquinolone performed in a one-pot fashion.

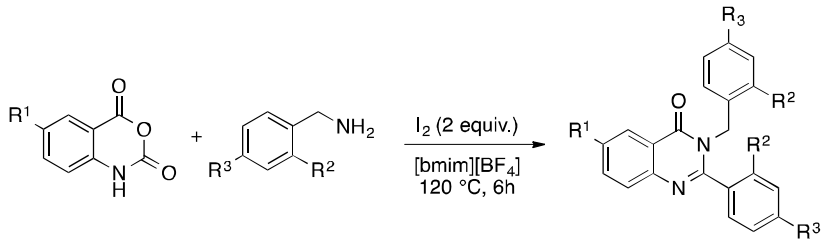


R=H, 3-CF_3, 4-NO_2, 4-CH_3

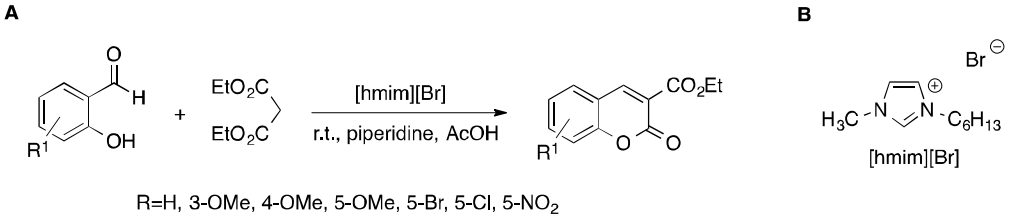
Scheme 23. Functionalization of indole with sulfonylhydrazides.

In another example, the synthesis on coumarins *via* Knoevenagel reaction was accomplished using the IL [hmim][Br] as solvent, as reported in Scheme 25.[46] The reactions were conducted at room temperature and excellent product yields were obtained, regardless of the electronic donating- or withdrawing nature of the

substituent on the salicyladheyde. However, no comparison with conventional solvents was provided, and no information on recyclability was given.

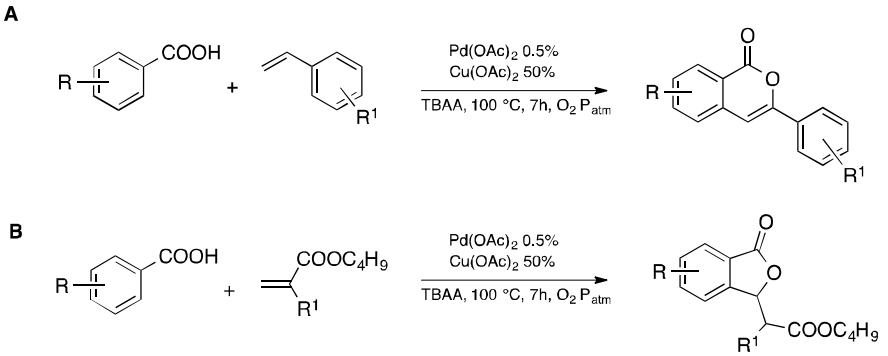


Scheme 24. Oxidative cyclization for the synthesis of 2,3-disubstituted quinazolinones.



Scheme 25. A) Synthesis of coumarins and B) IL used.

The synthesis of related compounds like isocoumarins was performed by reacting benzoic acids with styrenes in the presence of Pd(II) acetate as catalyst and Cu(II) acetate as terminal oxidant, in the aliphatic IL tetrabutylammonium acetate (TBAA), as reported in Scheme 26.[47] The yields obtained in the IL were higher than the ones obtained in conventional solvents like dimethylacetamide or imidazolium-based ILs. The nature of the anion of the copper salts also proved important, since Cu(II) salts with anions other than acetate led to poor yields and conversion. The scope of the reaction could be expanded to acrylates, which, reacting with benzoic acids, gave phthalides in good to excellent yields.

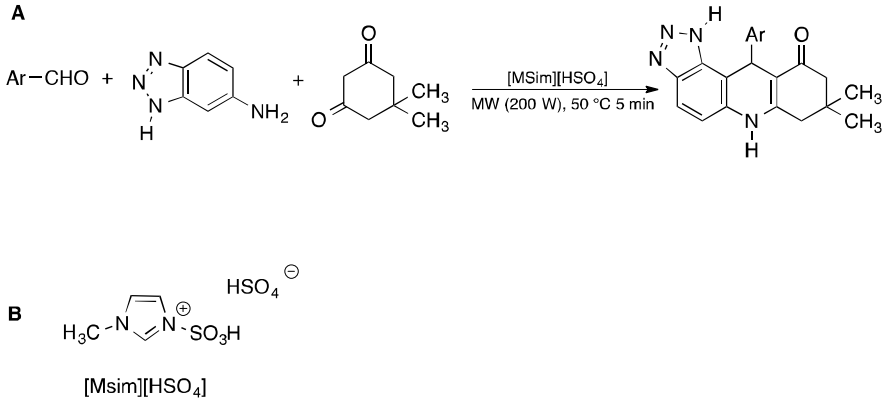


Scheme 26. A) Synthesis of isocoumarines and B) phathalides.

4. Synthesis of polyciclic and spirocyclic heterocycles

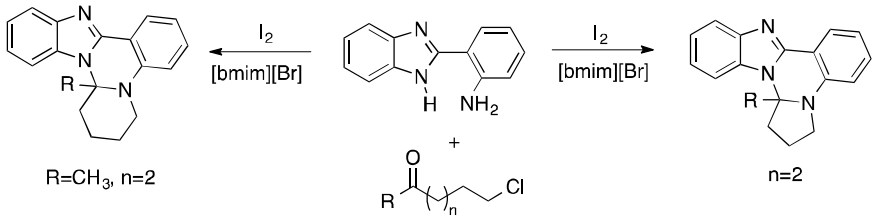
In a one-pot, multicomponent reaction promoted by non-conventional means of heating, tetrahydrotriaozoloacridines were obtained in the presence of the Brønsted acidic IL 3-methyl-1-sulfonic acid imidazolium hydrogensulfate [MSim][HSO_4] under microwave irradiation (MW) (Scheme 27).[48] The IL played the dual role of solvent and catalyst. Unlike what happened in ethanol, high yields, comprised between 76% and 94%, were obtained conducting the reaction in the IL, at 50 °C in 5 minutes. Comparison with results

obtained under conventional heating, revealed comparable yields, but MW activation induced a drastic reduction in reaction time, since 1 h was required to obtain similar yields under oil-bath heating. Moreover, the reaction showed a reasonable scope, with better results in the presence of aromatic aryl aldehydes bearing electron withdrawing substituent. Finally, after extraction with ethyl acetate, the IL could be reused further 5 times with no significant reduction in yield.



Scheme 27. A) Synthesis of tetrahydrotriaozoloacridines and B) IL used as catalyst and solvent.

The synthesis of pyrrolo[1,2-a]- or pyrido[1,2-a]benzo[4,5]imidazo[1,2-c]quinazoline derivatives was accomplished in the IL [bmim][Br], in the presence of iodine as catalyst, as reported in Scheme 28.[49] The cyclization in IL was performed at 80 °C, with reaction times ranging from 9 h to 13 h, depending on the halogenated ketone used as substrate, obtaining yield comprised between 86% and 92%. Comparison with conventional solvents such as toluene, DMF and acetonitrile, showed that the advantage of using the IL as solvent mostly consisted in a reduction of reaction temperature, rather than an increase in yield or recyclability, since no attempt to recycle the IL was reported.

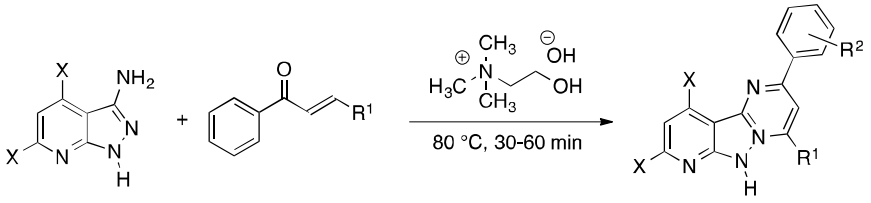


Scheme 28. Synthesis of pyrrolo[1,2-a]- and pyrido[1,2-a]benzo[4,5]imidazo[1,2-c]quinazoline derivatives.

The synthesis of pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine derivatives was successfully carried out employing the basic IL cholinium hydroxide as catalyst in a solventless reaction between α,β-unsaturated ketones with 1*H*-pyrazolo[3,4-b]pyridin-3-amines, shown in Scheme 29.[50] The reaction exhibited a wide scope, with good to excellent yields in all cases. The IL catalyst could be recycled three times without significant drop in yields, and the reaction could be performed in gram scale, with only a minor reduction in yield.

ILs have also proven highly efficient in the synthesis of spirocyclic scaffolds. The interest for this kind of heterocycles comes from the urgent need to develop antimicrobial having completely different structures, to face the increasing emergence of drug resistance. Diversity in structure can guarantee different mechanisms of action. In this context, spirocyclic scaffolds are very attractive for their three-dimensional structure, able to establish interactions with the three-dimensional binding sites, compared with planar heterocyclic compounds. Spirocyclic compounds can be obtained by means of a domino multicomponent 1,3-dipolar cycloaddition

strategy between azomethine ylide and dipolarophiles, in the presence of L-phenylalanine (Scheme 30).[51] The reaction was carried out in different solvents, with yields ranging from 40% to 49%. In the presence of an imidazolium-based IL, such as [bmim][Br], dispiroheterocyclic compounds were obtained through a one-pot, four-component cycloaddition reaction at 100 °C after 1 h, affording yields higher than 60%. The high efficiency of the process was ascribed to the dual role of the [bmim$^+$] cation, which forms hydrogen bonds with the carbonyl units of ninhydrin, increasing the electrophylicity of the carbonyl groups, and therefore accelerating the reaction. Different derivatives were obtained through the above procedure, and some of them exhibited significant antimicrobial activities towards Gram-positive bacteria. In particular, the 4-methyl derivative could also be effectively combined with streptomycin and vancomycin, showing outstanding synergistic activity against *E. Coli*. Docking simulation revealed that this compound strongly interacts with the binding site (binding energy=–39.576 kcal/mol), helping to have good pharmacological inhibitory activity towards microbial pathogens.

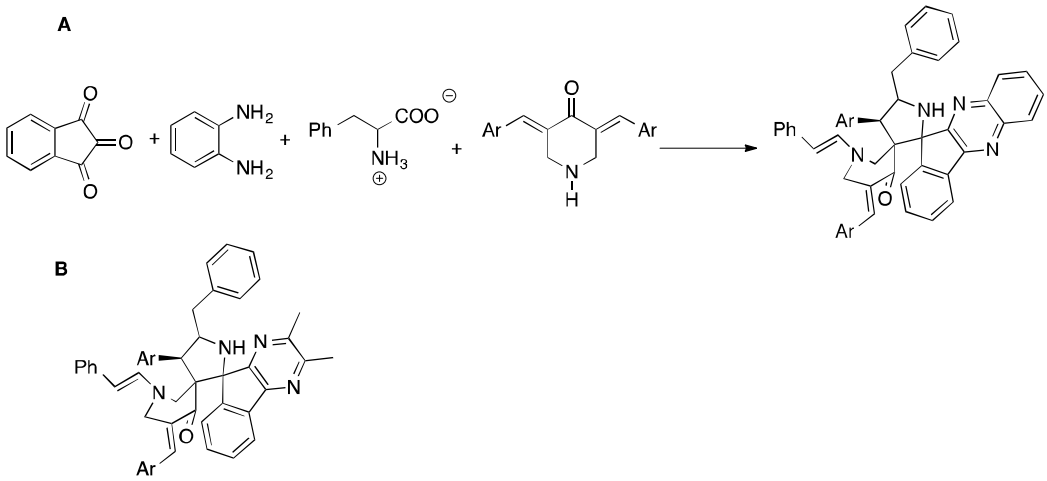


X=H, CH_3

R^1=Aromatic, Heteroaromatic, Aliphatic

R^2=H, CH_3, Cl

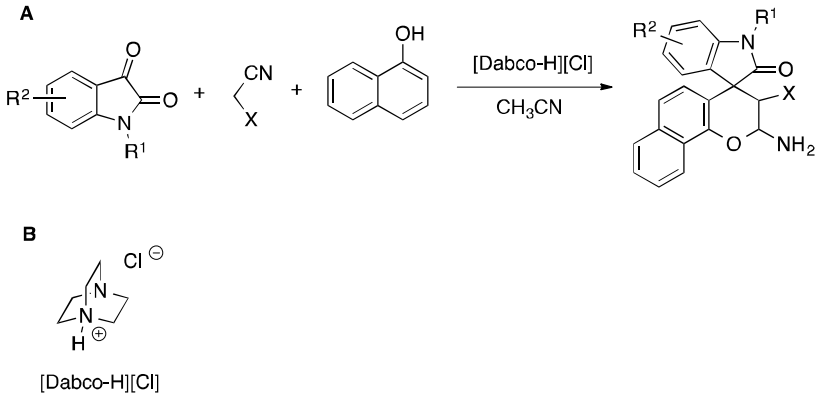
Scheme 29. Synthesis of pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine derivatives.



Scheme 30. A) Synthesis of dispiroheterocyclic compounds in [bmim][Br] and B) structure of the most active antimicrobial agent obtained.

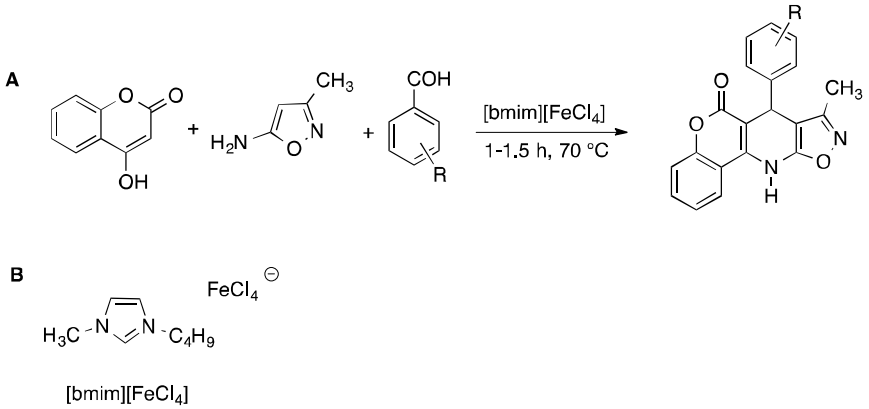
Xu et al. described a one-pot synthesis of spiro[2-amino-4*H*-pyrans] involving isatins, active methylenes and a wide range of carbonyl compounds, promoted by a protic IL, reported in Scheme31.[52] The reaction occurred with excellent yields with a broad scope, also using ninhydrines as substrates. Furthermore, the IL could be recycled 5 times without significant drop in yields. A mechanistic hypothesis was proposed, involving fast Knoevenagel condensation between the dicarbonyl compunds and the active methylene ones. This

intermediate then undergoes a Michael addition with the enolate formed by the activation of the third component by the IL. Finally, this latter intermediate affords the product by cyclization and tautomeric shift aided by the IL catalyst.



Scheme 31. A) Synthesis of spiro[2-amino-4*H*-pyrans] derivatives and B) IL catalyst.

A similar strategy was employed for the synthesis of dihydro-6*H*-chromeno[4,3-b]isoxazolo[4,5-e]pyridines using the IL [bmim][$FeCl_4$], acting both as solvent and catalyst (Scheme 32).[53] In general, the yields obtained in the IL were always significantly higher than the ones observed in conventional solvents. The IL could be reused 4 times without reduction in yields, and some of the compounds synthesized exhibited moderate antidiabetic activity.

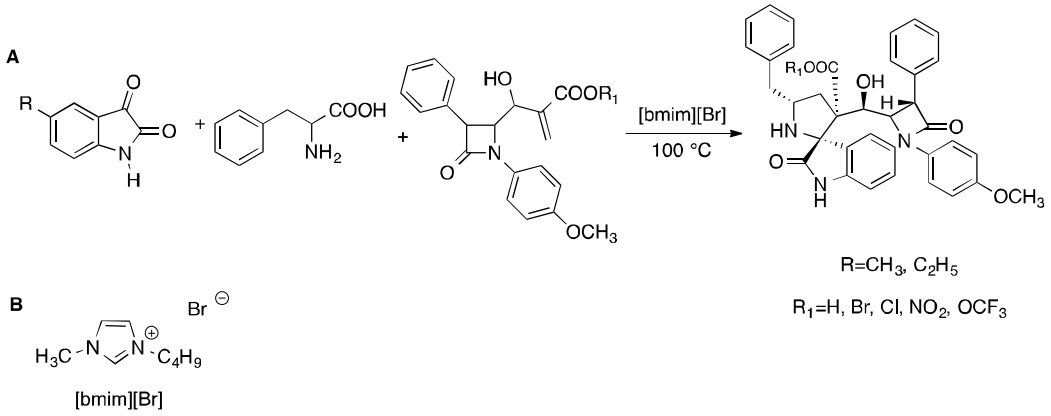


Scheme 32. A) Synthesis of dihydro-6*H*-chromeno[4,3-b]isoxazolo[4,5-e]pyridines and B) IL catalyst.

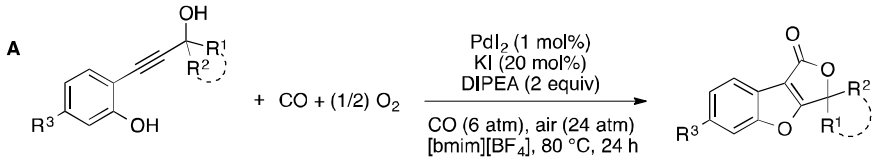
In another example, spirooxyndolepyrrolydine bearing a β-lactam functionality were prepared by means of a multicomponent [3+2]-cycloaddition carried out in the IL [bmim][Br] as solvent,[54] as shown in Scheme 33. The reaction showed a reasonable scope, with yields in the range 70%-90%. Using the IL as solvent allowed to obtain higher yields in lower times, compared with the conventional solvents used, such as ethanol, acetonitrile and 1,4-dioxane. Some of these compounds showed also antimicrobial activity against *Mycobacterium tuberculosis.*

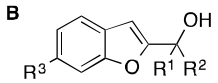
Replacing conventional solvents with ILs resulted in better selectivities and yields on the carbonylative double cyclization for the synthesis of furo[3,4-b]benzofuran-1(3H)-ones (Scheme 34).[55] In this reaction, the base deprotonates the phenolic group on the substrate, leading to a nucleophilic attack on the triple bond,

which is activated by coordination to the metal center. When the reaction was carried out in conventional organic solvents like acetonitrile and 1,2-dimethoxyethane, the formation of the furobenzofuranone product was accompanied by the occurrence of the benzofuran side product, derived from single cyclization (Scheme 34B). Conversely, when the solvent used was the IL [bmim][BF_4], the furobenzofuranone derivative was obtained in higher yields and as the sole product. Furthermore, the reaction showed a good scope and the IL-catalyst system could be recycled for seven consecutive runs, with no significant loss in yield, irrespective of the substituent of the substrate considered.



Scheme 33. A) Multicomponent cycloaddition and B) IL used.





Scheme 34. A) Carbonylative double cyclization reaction and B) benzofuran side product.

5. Conclusions

In this chapter, we provided an overview on recent works on the use of ILs as solvents and/or catalysts for the synthesis of heterocyclic compounds of different complexity. Most of the works highlight the beneficial effect of ILs over conventional solvents mainly in terms of enhanced yield or reaction rates. In some instances, IL also allow the reactions to be carried out in milder conditions. In some cases, drastic reduction of reaction times and/or temperatures are achieved when coupling ILs with non-conventional means of activation like ultrasounds or microwave irradiation. The vast majority of the work discussed herein, show that the recyclability of the IL solvent is a recurring theme, regardless of the type of reaction or heterocyclic scaffold involved.

It is also worth mentioning that works delving deeper on the mechanistic pathways operating in ILs show that the regioselectivity can be effectively enhanced with judicious choice of ions. Finally, the organized

nature of such solvents exerts a significant influence on reactivity and can be usefully harnessed in the synthesis of heterocyclic compounds.

Acknowledgements

We thank the University of Palermo for financial support.

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