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# Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis

Nicolas Isambert,<sup>a</sup> Maria del Mar Sanchez Duque,<sup>a</sup> Jean-Christophe Plaquevent,<sup>b</sup> Yves Génisson,<sup>b</sup> Jean Rodriguez\*<sup>a</sup> and Thierry Constantieux\*<sup>a</sup>

The efficiency of a chemical synthesis can be nowadays measured, not only by parameters like selectivity and overall yield, but also by its raw material, time, human resources and energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved. The development of multicomponent reactions (MCRs) in the presence of task-specific ionic liquids (ILs), used not only as environmentally benign reaction media, but also as catalysts, is a new approach that meet with the requirements of sustainable chemistry. The aim of this *tutorial review* is to highlight the synergistic effect of the combined use of MCRs and ILs for the development of new eco-compatible methodologies for heterocyclic chemistry.

## Introduction

In the context of sustainable chemistry,<sup>1</sup> the design and development of sequences allowing highly selective access to elaborated molecular scaffolds while combining structural diversity<sup>2</sup> with eco-compatibility,<sup>3</sup> are great challenges for organic chemists. Thanks to their ability to build one product in a single operation from three or more reactant molecules with high atom-economy<sup>4</sup> and multiple-bond-forming efficiency,<sup>5</sup>

multicomponent reactions (MCRs),<sup>6</sup> are now well-established approaches to reach this near ideal goal.<sup>7</sup> Due to these environmental concerns, investigation of alternatives to conventional organic solvents resulted in a considerably growing interest in the use of room temperature ionic liquids (RTILs).<sup>8,9</sup> Furthermore, thanks to their user-friendly and adjustable physico-chemical properties, RTILs have found numerous applications not only as environmentally benign reaction media, but also as catalysts and reagents.<sup>10</sup> From this perspective, combining synthetic potentialities of MCRs with the dual properties of RTILs as solvents and promoters results in the emergence of promising strategies for the development of valuable eco-compatible organic synthesis procedures.<sup>11</sup> This review aims at illustrating this concept through recent selected examples and to highlight the synergistic use of MCRs and RTILs for an eco-compatible heterocyclic chemistry.<sup>12</sup> This article will be divided in four sections.

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Nicolas Isambert

Nicolas Isambert was born in Albi (France) on 22nd August 1978. After studying chemistry at the University of Montpellier, he completed his PhD under the supervision of Dr N. J. Westwood at St Andrews University, Scotland. After a postdoctoral position in Barcelona under the supervision of Professor Rodolfo Lavilla where he was investigating development of multicomponent reactions, he moved back to France in Professor J. Rodriguez lab to develop multicomponent reactions in ionic liquids. He is currently at the University of Orléans in a collaboration with Servier. His research interest includes multicomponent reaction, heterocyclic chemistry, medicinal chemistry and green chemistry.



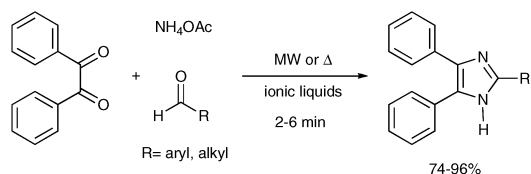
Maria del Mar Sanchez Duque

Maria del Mar Sanchez Duque was born in Cali, Colombia, in August 1985. She obtained her BSc in chemistry in 2006 and her MSc in 2008 both from the University of Montpellier (France). Currently, she is pursuing her PhD under the supervision of professors Thierry Constantieux and Jean Rodriguez at the University Paul Cézanne in Marseille (France). Her research focuses on multicomponent reactions and asymmetric synthesis.

The first one concerns the use of ionic liquids as alternative solvents for organic transformations, the second one presents the use of ionic liquids as catalysts in organic chemistry, and the third one deals with ionic liquids as immobilizing phases. Finally, the last part of this review discusses the challenge of relative and absolute stereochemical control in the combined use of MCR and RTILs.

### Ionic liquids as alternative solvents for MCRs

This section deals with MCRs performed in ionic liquid solutions. The capacity of ionic environments to generate internal pressure and to promote the association of reactants in solvent cavities render them excellent media for multiple bond-forming transformations. Their wide solvating capacity and liquid range also clearly render them suitable solvents for multicomponent processes.



**Scheme 1** Microwave-assisted three-component synthesis of 2,4,5-trisubstituted imidazoles.

### Condensations with functionalized carbonyl compounds

The synthesis of imidazoles *via* MCRs involving an aldehyde, a source of ammonia and a 1,2-dicarbonyl reactant is a useful process. However, harsh conditions such as several hours of reflux in AcOH or H<sub>2</sub>SO<sub>4</sub> are usually applied in standard methods that suffer from low yields. The use of additional acidic catalysts is also required under solvent-free conditions. Interestingly, the combined use of microwave irradiation and



**Jean-Christophe Plaquevent**

*Jean-Christophe Plaquevent was born in 1953 in Normandy, France. In 1977 he joined the CNRS at Rouen University, where he completed his thesis in 1980 in the laboratory of Professor P. Duhamel. He had postdoctoral experiences as a research associate with Professor A. Eschenmoser at ETH Zürich and at Rouen University where he studied molecular biology with Dr H. Vaudry. In 2007, he moved to Toulouse University, where he is still employed by CNRS as research director. His research interests focus on asymmetric synthesis, pharmaceutical compounds, amino acid and peptide chemistry, and ionic liquid methodologies.*



**Yves Génisson**

*Yves Génisson was born in Boulogne sur Seine, France, in 1963. He completed his PhD in 1992 at the ICSN in Gif sur Yvette under the supervision of Dr C. Marazano. After working for two years at the Merck-Frosst Centre of Therapeutic Research in Montréal, Canada, he joined the CNRS as a researcher in the group of Dr A. E. Greene in Grenoble, France. In 1998, he moved to the Université Paul Sabatier of Toulouse where he completed his Habilitation in 2003. He is currently working both in the field of chiral ionic liquids and asymmetric synthesis of bioactive compounds.*



**Jean Rodriguez**

*Jean Rodriguez was born in Cieza (Spain) in 1958 and in 1959 his family emigrated to France. After studying chemistry at the University Paul Cézanne in Marseille (France), he completed his PhD as a CNRS researcher with Prof. B. Waegell and Prof. P. Brun in 1987. He completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-6263-iSm2. His research interests include the development of domino and multicomponent reactions, and their application in stereoselective synthesis. In 1998 he was awarded the ACROS prize in Organic Chemistry, and in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society.*



**Thierry Constantieux**

*Thierry Constantieux was born in Pau, France, on 6 May 1968. After studying chemistry at the University Bordeaux I, he completed his PhD under the supervision of Dr J.-P. Picard and Dr J. Dunoguez in 1994. He completed his Habilitation in 2004, at the University Paul Cézanne, in Marseille, where he is currently Professor of Organic Chemistry. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially domino multicomponent reactions from 1,3-dicarbonyl compounds, and their applications in heterocyclic chemistry.*

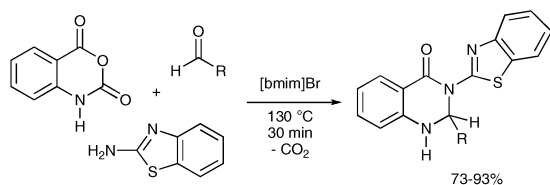
protonated 1-alkylimidazoles, referred to as Brønsted acidic ionic liquids, in the one-pot condensation with alkyl, aryl aldehydes and ammonium acetate in refluxing ethanol allowed Xia *et al.* to improve the synthesis of 2,4,5-trisubstituted imidazoles in significantly reduced reaction times without additional acidic catalysts (Scheme 1).<sup>13</sup>

The recyclability of [C<sub>7</sub>mim]BF<sub>4</sub> as the reaction medium was demonstrated by systematically studying reactions involving four different aldehydes. After four consecutive cycles, the authors observed that the products of interest were still obtained in efficient synthetic yields. Alternatively, an eco-friendly procedure for the same reaction, using tetrabutylammonium bromide as a neutral ionic liquid catalyst, has been reported.<sup>14</sup>

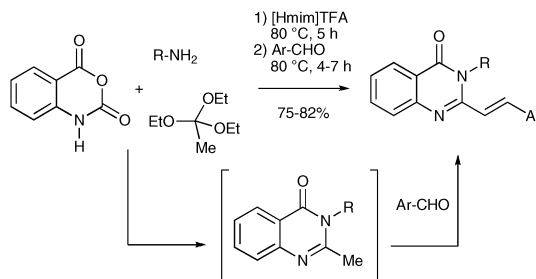
Benzimidazole and benzothiazole derivatives are important classes of heterocyclic compounds exhibiting a wide spectrum of pharmacological properties. Among the numerous synthetic approaches, an efficient multicomponent sequence in ionic liquids has been developed for the synthesis of new 2,3-dihydroquinazolin-4(1*H*)-ones.<sup>15</sup> Indeed, the reaction of 2-amino-benzothiazole with isatoic anhydride and various aldehydes was studied in various ionic solvents, and [bmim]Br revealed most appropriate (Scheme 2). The reaction proceeds well with a wide variety of aldehydes, and the desired products are formed in 0.5 h with yields ranging from 73 to 93%. Even when the reaction medium is recycled up to five times, the heterocycles are obtained in comparable yields. It is important to note that the reaction yielded only traces of the desired product in absence of the ionic liquid, even at high temperatures.

Isatoic anhydride was also recently involved in a three-component reaction carried out in the presence of an acidic ionic liquid, allowing the first direct access to 2-styryl quinazolinones under environmentally benign conditions.<sup>16</sup> Thus, the one-pot condensation of isatoic anhydride with triethyl orthoacetate and various primary amines in 1-methylimidazolium trifluoroacetate ([Hmim]TFA) led to the formation of the corresponding 2-methylquinazolinones. Subsequent addition of one equivalent of an aromatic aldehyde resulted in the one-pot formation of the expected 2-styryl substituted products in good overall yields (Scheme 3). The success of this one-pot process confirmed that the acidic ionic liquid [Hmim]TFA could act as an efficient reaction medium for heterocyclic synthesis<sup>17</sup> as well as an efficient promoter of Knoevenagel condensation of C–H acid compounds with aromatic aldehydes.<sup>18</sup>

Another important class of biologically relevant heterocycles has been efficiently synthesized in ionic liquids. 1-Pyridylimidazo[1,5-*a*]pyridines are usually generated in classical



**Scheme 2** Three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in [bmim]Br.



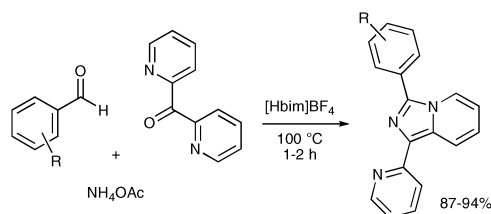
**Scheme 3** One-pot synthesis of 2-styryl quinazolinones in acidic ionic liquid.

organic solvents and the synthetic protocols necessitate harsh conditions, long reaction times, and low conversions are observed. It was reported that these heterocycles can be accessed through a one-pot condensation of 1,2-dipyridylketone, aromatic aldehydes and ammonium acetate in various ionic liquids, in the absence of any added catalyst (Scheme 4).<sup>19</sup> The Brønsted acidic ionic liquid 1-butylimidazolium tetrafluoroborate, [Hbm]BF<sub>4</sub>, was found to be the medium of choice, and under the optimized conditions, the reaction was driven to completion after a couple of hours at 100 °C. Moreover, yields are dramatically increased compared to similar reactions run in conventional organic solvents. Interestingly enough, the authors observed a good correlation between the basicity of the anion of the ionic liquid and the efficiency of the transformation. As the same phenomenon was observed with increasing polarity of the medium, the authors concluded that ionic liquid both acts as a reaction medium and as a promoter.

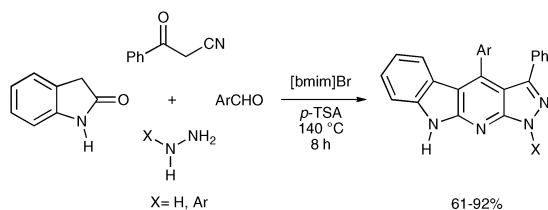
Due to their interesting biological properties,  $\alpha$ -carboline, *i.e.* pyrido[2,3-*b*]indoles have attracted considerable interest. A green and efficient four-component synthesis of  $\alpha$ -carboline derivatives in ionic liquids has been recently reported (Scheme 5).<sup>20</sup> Among the different advantages related to the use of ionic liquids, it is important to note that a similar reaction conducted in organic solvents only afforded traces of the desired products.

#### Condensations with 1,3-dicarbonyl compounds and analogues

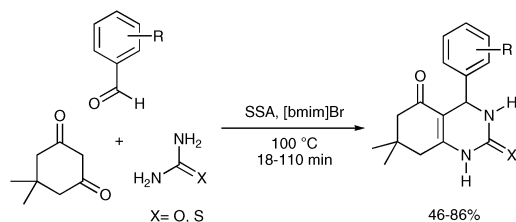
The Biginelli reaction is one of the fundamental MCRs yielding dihydropyrimidines (DHPMs) from ureas, aldehydes and 1,3-dicarbonyls. It is often catalyzed by Brønsted acids, and such activation is also necessary when ionic liquids are used as reaction media. For example, it was reported that quinazolin-2,5-dione derivatives may be efficiently accessed *via* the reaction between dimedone, aldehydes and urea or thiourea



**Scheme 4** Ionic liquid promoted one-pot synthesis of 1-Pyridylimidazo[1,5-*a*]pyridines.



**Scheme 5** Ionic liquid promoted four-component synthesis of  $\alpha$ -carbolines.



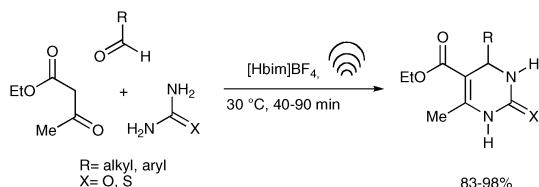
**Scheme 6** Combination of an ionic liquid and an acid solid catalyst for the one-pot synthesis of Biginelli-type scaffolds.

using a combination of [bmim]Br and silica sulfuric acid (SSA) as a solid acid catalyst (Scheme 6).<sup>21</sup>

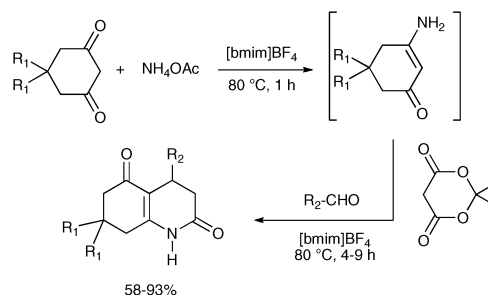
Products were obtained in moderate to good yields within short reaction times under conventional heating conditions. Comparing their results with that of similar reactions ran in ethanol,<sup>22</sup> the authors showed that yields were considerably increased with the new protocol, the reaction times being also dramatically reduced. Moreover, the reaction medium could be recycled four times keeping yields around 70%.

The use of additional acid catalyst for activation of the Biginelli reaction is obviated when the MCR is conducted in a Brønsted acidic ionic liquid. DHPMs have been synthesized in [Hbm]BF<sub>4</sub> under ultrasound irradiation with excellent yields and short reaction times at ambient temperature (Scheme 7).<sup>23</sup> On the basis of NMR and IR analyses, the authors demonstrated that the  $-NH$  proton, associated with the Brønsted acidity of the ionic liquid, was able to bond with the carbonyl oxygen of the aldehyde as well as that of the  $\beta$ -keto ester, thus activating both partners. Thereby, the IL not only acts as a favourable reaction medium but also as a promoter of the MCR. It is important to note that the combined synergistic effects of acidic IL and ultrasound activation account for the reaction reaching completion at room temperature in short times.

Another well-established MCR is the Hantzsch reaction involving 1,3-dicarbonyl compounds, aldehydes and primary



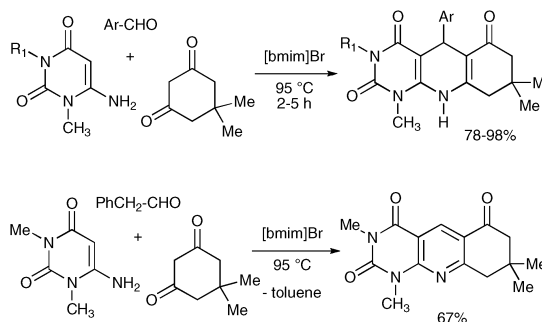
**Scheme 7** Synergistic effect of the use of acidic IL under ultrasound irradiation for the free-acid catalyst Biginelli reaction.



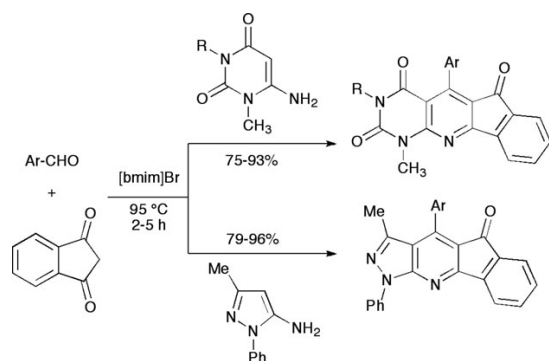
**Scheme 8** Hantzsch-type reaction in ionic liquid.

amines, leading to dihydropyridines (DHPs). In 2006, Fan *et al.* reported the sequential synthesis of DHPs through a four-component reaction in ionic solvents (Scheme 8).<sup>24</sup> This method describes the use of [bmim]BF<sub>4</sub> for the quantitative pre-formation of the enaminoketone on which the other partners of the MCR are added. After several hours at 80 °C, the nitrogen containing heterocycle was isolated in moderate to excellent yields. Due to the specific role of Meldrum's acid and ammonium acetate, only the variation on the aldehyde and the 1,3-diketone has been investigated. The reaction was run in a successful manner with either cyclic or acyclic  $\beta$ -dicarbonyl partners, the latter giving the lowest yields. This ionic liquid method improves the synthesis of DHP derivatives otherwise facing unsatisfactory yields and long reaction times. The important issue of recycling the reaction media is demonstrated in this work as the recovery of the IL allowed the synthesis of DHPs after four cycles without a drop in efficiency.

A related three-component reaction involving a preformed cyclic  $\beta$ -enaminocarbonyl in various ionic liquids can also give access to polycyclic compounds in high yields, overcoming some problems previously faced with classical volatile organic solvents. Thus, the reaction between 6-aminopyrimidine-2,4-dione, dimedone and various aromatic aldehydes in [bmim]Br delivered in less than 5 h the corresponding pyrimido-[4,5-*b*]quinolines easily isolated in high yields (Scheme 9).<sup>25</sup> Interestingly enough, when phenylacetaldehyde was used in this sequence, the corresponding oxidized product was isolated after elimination of toluene and formation of the pyridine moiety.



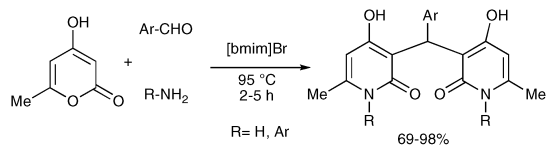
**Scheme 9** Three-component synthesis of pyrimido[4,5-*b*]quinolines.



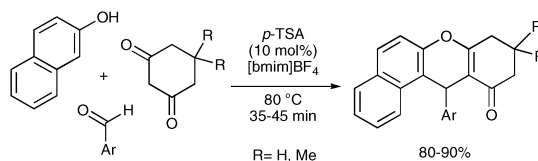
**Scheme 10** Multicomponent synthesis of pyrido- and pyrazolo-pyrimidine derivatives in ionic liquids.

Alternatively, under similar reaction conditions, the condensation of 1,3-indanedione with aromatic aldehydes and either 6-aminopyrimidine-2,4-dione or 5-amino-3-methyl-1-phenylpyrazole progressed to the efficient formation of indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine<sup>25</sup> or indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-5(1*H*)-one<sup>26</sup> derivatives, respectively (Scheme 10). Compared with other classical methods, this environmentally benign procedure has the advantages of higher yields and easier work-up.

6-Methyl-4-hydroxypyran-2-one constitutes also an interesting 1,3-dicarbonyl starting material with unusual reactivity in ionic liquids. Indeed, when this substrate is reacted with an aldehyde and a primary amine or ammonium acetate, the sequence evolves through an intermolecular condensation with concomitant transamidation of the lactone ring to form bislactam systems (Scheme 11).<sup>27</sup> The best yields were obtained in [bmim]Br. Aromatic and aliphatic aldehydes were good partners for this MCR, and products were obtained with high yields in less than 2 h. However, the nature of the amines is limited to ammonia and anilines, while benzylamine for example led to complex mixture of products. Recycling the ionic liquid five times produced the desired product with similar yields up to 95%. Finally, it is noteworthy that only traces of product are detected in methanol, and no reaction was observed in acetone, acetonitrile, chloroform, water or acetic acid, highlighting the fact that the participation of the IL is again of critical importance. A variation of this reaction has been described recently in [bmim]BF<sub>4</sub> by changing the amine partner for  $\beta$ -naphthol, and using *p*-TSA as catalyst. The reaction was studied on 1,3-cyclohexanedione and dimedone and differently substituted aromatic aldehydes. The electronic character of the substituents had no impact on the reaction giving access to tetrahydrobenzoxanthenone derivatives with high yields in less than 4 h (Scheme 12).<sup>28</sup>



**Scheme 11** Synthesis of bislactam systems.



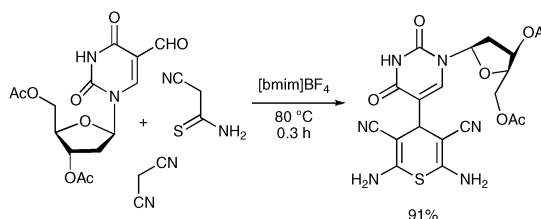
**Scheme 12** *p*-TSA-catalyzed synthesis of tetrahydrobenzoxanthenone derivatives in ionic liquids.

Finally, ionic liquid proved to be an efficient medium for the three-component reaction between cyanothioacetamide, malononitrile and various aldehydes leading to the one-pot, catalyst-free synthesis of thiopyran derivatives.<sup>29</sup> A rapid screening of classical solvents concluded in the benefit of [bmim]BF<sub>4</sub> as best solvent, best yields and shorter reaction times. Moreover, selectivity was increased and work-up was simplified. In addition, the ionic liquid can be easily recovered and reused in at least four consecutive runs without a decrease of efficiency. The potentiality of this methodology was illustrated by the synthesis of a bioactive pyrimidine nucleoside-thiopyran hybrid (Scheme 13).

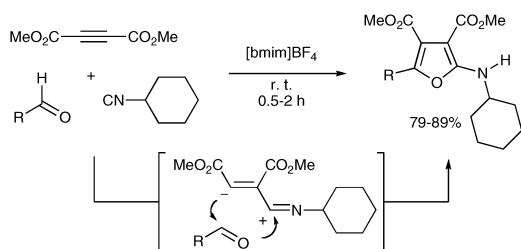
#### Condensation with isocyanides

Although isocyanide-based MCRs are widely developed in conventional solvents,<sup>30</sup> especially the Ugi and the Passerini reactions, they have received recent attention in ionic liquids. In this context, the first example in heterocyclic chemistry has been reported by Yadav *et al.* in 2004 for the synthesis of polysubstituted 2-aminofuran derivatives. Accordingly, the three-component reaction of cyclohexyl isocyanide with dimethyl acetylenedicarboxylate (DMAD) and various aromatic or aliphatic aldehydes went to completion in less than 2 h when ran in ionic liquids, affording the expected heterocycles in high yields (Scheme 14).<sup>31</sup> The hydrophilic [bmim]BF<sub>4</sub> was found to give the best results, whereas either hydrophobic [bmim]PF<sub>6</sub> or organic solvents gave poor yields, even under forced conditions. According to the authors, this enhanced reactivity in ionic liquids may be due to the formation of a zwitterionic intermediate, resulting from the addition of the isocyanide on DMAD.

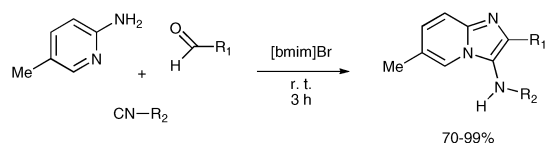
The Bienaymé<sup>32</sup>–Blackburn<sup>33</sup>–Groebke<sup>34</sup> MCR, consisting of the condensation of an aldehyde, an isocyanide and a 2-aminoazine in the presence of a strong protic acid, allows the synthesis of imidazo[1,2-*a*]pyridines. These heterocycles constitute an important class of pharmaceutical product with a wide spectrum of biological activities.<sup>35</sup> Experimentally, complications such as long reaction times or use of strongly



**Scheme 13** Three-component synthesis of thiopyran derivatives in [bmim]BF<sub>4</sub>.



**Scheme 14** Ionic liquids-promoted three-component synthesis of 2-aminofurans.



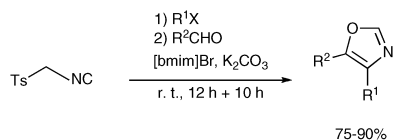
**Scheme 15** Synthesis of 3-aminoimidazo[1,2-*a*]pyridines in [bmim]Br.

acidic cation exchange resin for isolation are faced when the reactions need to be pushed to completion. Again, ionic liquids have brought an improvement on top of their eco-compatibility, as recently illustrated by the group of Shaabani (Scheme 15).<sup>36</sup> Indeed, when the reaction between an aldehyde, an isocyanide and 2-amino-5-methylpyridine is carried out without [bmim]Br, the corresponding 3-aminoimidazo[1,2-*a*]pyridine is isolated in 25% yield after 12 h at room temperature, whereas the same reaction conducted in [bmim]Br proceeds in very high conversion in only 3 h. Typically, yields are obtained in the range of 70 to 99%.

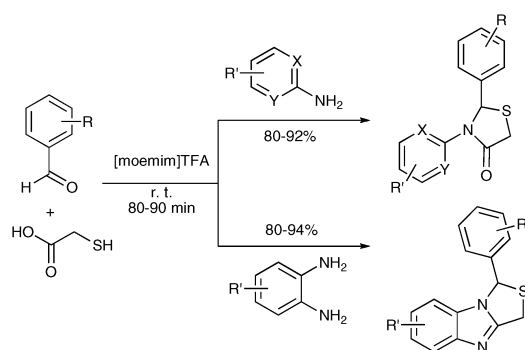
Finally, another example illustrating the use of isocyanides in ionic liquids is the synthesis of oxazoles *via* the van Leusen reaction<sup>37</sup> with tosylisocyanide (TSMIC). Despite the fact that the reaction conditions are not truly considered as those of a MCR but a one-pot transformation, the process is interesting to mention. The alkylating step followed by *in situ* reaction with an aldehyde provides oxazoles in 75–90% yields. (Scheme 16).<sup>38</sup> The authors looked at the recyclability of [bmim]Br employed as the reaction solvent. A slight decrease in the yield was observed throughout the six consecutive runs, dropping to 64%.

### Miscellaneous

A reaction that we could not classify among the other groups is the microwave assisted sequence involving a heteroaromatic amine or 1,2-phenylenediamine, 2-mercaptoacetic acid and aromatic aldehydes for the regioselective synthesis of substituted thiazolidinones or benzimidazoles in ionic liquids (Scheme 17).<sup>39</sup> Two different media have been evaluated, and 1-methoxyethyl-3-methylimidazolium trifluoroacetate



**Scheme 16** One-pot van Leusen synthesis of 4,5-disubstituted oxazoles in ionic liquids



**Scheme 17** One-pot syntheses of substituted thiazolidinones and benzimidazoles in ionic liquids.

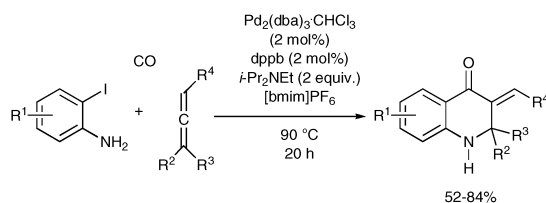
[moemim]TFA revealed to be a better solvent compared to [bmim]BF<sub>4</sub>, this difference being probably due to the ability of the former to develop hydrogen bonds with the amine reactant. Regarding the recyclability of the ionic liquid, the authors showed that IL can be successfully reused, making this procedure advantageous over more conventional ones.

Transition-metal-complex-catalyzed MCRs may also be conducted in ionic liquids, with enhanced efficiency compared to classical organic solvents. For example, the [bmim]PF<sub>6</sub>-promoted palladium-catalyzed cyclocarbonylation of *o*-iodoanilines and allenes afforded the corresponding 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in moderate to excellent yields under a low pressure of CO (Scheme 18).<sup>40</sup> Similar reactions using benzene as solvent led to the same products, but with lower yields. The recyclability of the reaction media containing the catalytic system was demonstrated by the authors, since the ionic liquid containing the metal catalyst and the ligand could be reused 4–6 times without significant decrease in the yields.

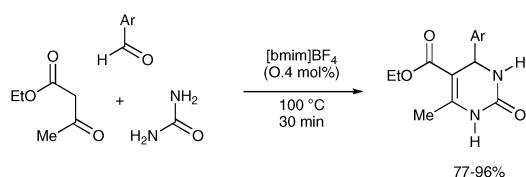
### Ionic liquids as catalysts for MCRs

This section is dedicated to MCRs induced by catalytic or substoichiometric amounts of ionic liquids. None of the following examples contain ionic liquids as solvent for the reaction. Most of the ILs presented below are thus, as commonly said, task-specific ionic liquids (TSIL), which are tailor-made for their acidic/basic properties. All the selected examples involve the use of 1,3-dicarbonyl compounds and analogues as reactants.

As described in the initial work, the Biginelli reaction requires harsh conditions, *i.e.* the use of protic or Lewis acids



**Scheme 18** Palladium-catalyzed multicomponent synthesis of 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in [bmim]PF<sub>6</sub>.

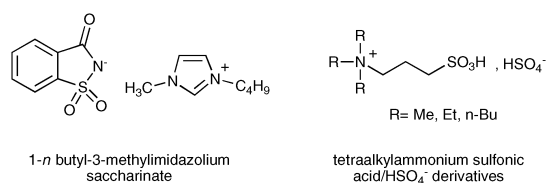


**Scheme 19** Ionic liquid-catalyzed solvent-free Biginelli reaction.

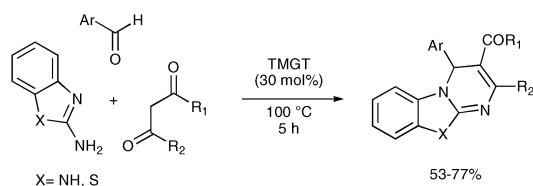
and generally high temperatures. An abundant literature covers all these aspects including a recent compilation of a large number of catalytic systems.<sup>41</sup> The main goal of recent investigations aims at performing this MCR under milder conditions, increasing the yields and widening the scope of partners. In this context, Pend and Deng were the first to report the use of ionic liquids as catalyst for the development of the Biginelli reaction under solvent-free and neutral conditions. Thus, in the presence of 0.4 mol% of [bmim]BF<sub>4</sub> or [bmim]PF<sub>6</sub>, the reaction between urea, ethylacetoacetate and various aromatic aldehydes led to the corresponding DHPs in high yields, after only 30 min at 100 °C (Scheme 19).<sup>42</sup> It is important to note that both cation and anion of the ionic liquid play an important role, since no reaction was observed using either [bmim]Cl or *n*-Bu<sub>4</sub>Cl as catalyst. In an even more eco-friendly protocol, Ming *et al.* reported that the Biginelli reaction could be performed with high conversion under solvent-free conditions in the presence of halogen-free and non-toxic ionic liquids as catalyst, such as 1-*n*-butyl-3-methylimidazolium saccharinate, [bmim]Sac (Fig. 1).<sup>43</sup> Interestingly, the same reaction with 0.4 mol% of catalyst performed under homogeneous conditions using a volatile organic solvent such as THF or DCM was totally unproductive. Similarly, protic solvents such as H<sub>2</sub>O and EtOH were not much more efficient, lacking in selectivity and leading to poor conversion.

Some other halogen-free ionic liquids such as acyclic tetraalkylammonium sulfonic acid/HSO<sub>4</sub><sup>-</sup> derivatives (Fig. 1), previously described for the Mannich reaction,<sup>44,45</sup> have been shown to catalyse the Biginelli reaction in aqueous media.<sup>46</sup> For example, in the presence of 20 mol% of one of these TSILs, the DHPMs are obtained in less than 15 min, with a large scope of all three components. The use of Brønsted acidic ionic liquid at 90 °C could have been a limitation with respect to functional group tolerance, but the authors showed that ether, ester, nitro, hydroxyl and halide groups were unaffected by the reaction conditions, allowing incorporation of diversity around the six membered-ring. The reaction media have been recycled up to five times and very high yields were obtained in the six consecutive runs, ranging from 90 to 94%.

In view of performing Biginelli transformations on a large-scale, and under eco-compatible conditions, ionic liquids



**Fig. 1** Task-Specific Ionic Liquids (TSILs) used in MCRs.



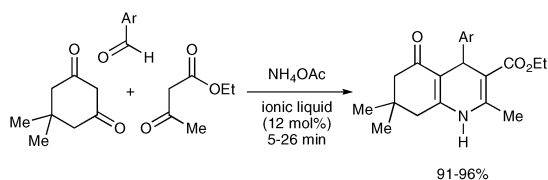
**Scheme 20** TMGT-catalyzed Biginelli-like reaction for the synthesis of 4*H*-pyrimido[2,1-*b*]benzazoles systems.

immobilized on Merrifield resin have been developed as catalysts.<sup>47</sup> Results published in 2005 by Wang *et al.* showed that polymer-supported [bmim]PF<sub>6</sub> performed very well when mixing aromatic aldehydes, ethyl acetoacetate and urea. At 100 °C for 2 h in acetic acid, the yield reached 98% and the recycled catalyst promoted the reaction even after five runs with very high conversion. In a Biginelli-type reaction involving 2-aminobenzimidazole or 2-aminobenzothiazole as urea or thiourea synthetic equivalents (Scheme 20), tetra-methylguanidinium trifluoroacetate (TMGT) acts as catalyst under solvent-free conditions, rendering the reaction an environmentally benign process where the use of volatile organic solvents is only required for the recrystallization of the crude product precipitated out from water.<sup>48</sup> The role of the ionic catalyst is essential to reach acceptable yields ranging from 53 to 77% with *p*-substituted aromatic aldehydes and β-ketoesters. The same entity has been recycled three times and yields decreased slightly from 66 to 55% throughout the recycling.

The use of ionic liquids as catalyst under solvent-free conditions also demonstrated interest in the four-component Hantzsch reaction for the synthesis of polyhydroquinoline derivatives. In 2004, Ji *et al.* reported that a catalytic amount of [hmim]BF<sub>4</sub> without solvent shortened the reaction times to a few minutes at 90 °C, increasing the yields up to 96%, the effect being already marked at room temperature (Scheme 21).<sup>49</sup> Aliphatic and aromatic aldehydes allowed the reaction to reach completion with excellent yields, regardless of the electronic nature of the substituent. Finally, several ionic liquids, with Br<sup>-</sup>, PF<sub>6</sub><sup>-</sup> or BF<sub>4</sub><sup>-</sup> as anions as well as [hmim] or [C<sub>10</sub>mim] as cations, are also efficient catalysts for this reaction.

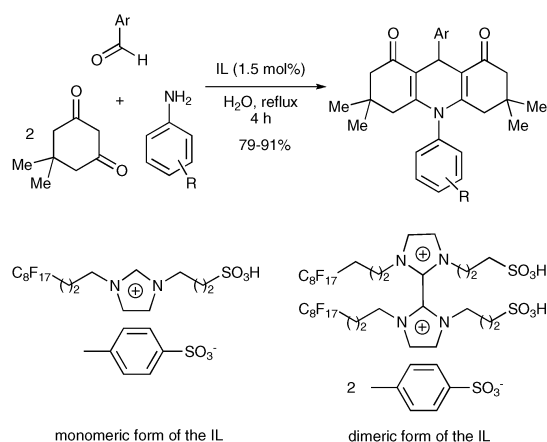
A related transformation with anilines in place of ammonium acetate, involving two equivalents of dimedone, has been developed under aqueous conditions for the synthesis of acridines. The catalytic system is a Brønsted acidic ionic liquid containing perfluoroalkyl tails either in monomeric or dimeric version (Scheme 22).<sup>50</sup>

After optimization, the use of 1.5 mol% of the dimeric catalyst in water at reflux for 4 h provided the expected



**Scheme 21** Ionic liquid-catalyzed four-component synthesis of polyhydroquinoline derivatives.

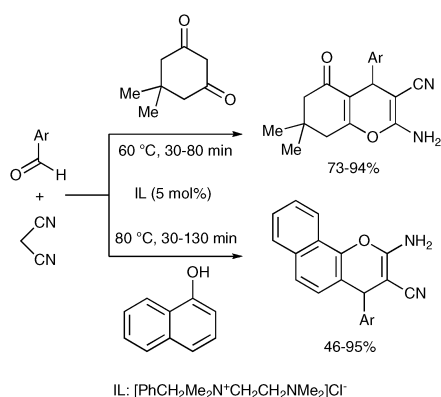




**Scheme 22** Brønsted acidic ionic liquid-catalyzed synthesis of acridines in water.

products in yields ranging from 79 to 91%. The catalytic medium can be recycled without significant loss of activity. The choice of aromatic aldehydes is not restricted by the electronic nature of the substituent, whereas the obtention of acridines is limited to nucleophilic anilines such as *para*-toluidine and *para*-anisidine.

The synthesis of 4*H*-benzo[*b*]pyran derivatives has also been proposed by means of a basic ionic liquid-catalyzed three-component approach involving malononitrile, aromatic aldehydes and dimedone. The conventional method, requiring the use of refluxing DMF or acetic acid, lead to low yields and renders the isolation step troublesome. Other procedures have been described but all of them suffer at least from one limitation. Alternatively, it has been found that a small amount of *N,N*-dimethylaminoethylbenzyl-dimethylammonium chloride catalyzed a rapid and high yielding solvent-free transformation at 60 °C with a wide variation of the aldehyde partner (Scheme 23).<sup>51</sup> The catalyst can also be recycled without losing its catalytic activity after four reuses. The same authors described in 2008 the syntheses of 2-amino-2-chromenes using the same catalytic ionic liquid under solvent-free conditions,  $\alpha$ -naphthol replacing dimedone as the third



**Scheme 23** Basic ionic liquid-catalyzed three-component synthesis of 4*H*-benzo[*b*]pyran and 2-amino-2-chromene derivatives.

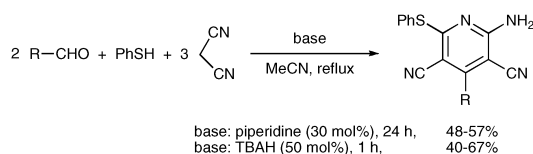
component (Scheme 23).<sup>52</sup> Following an eco-friendly approach, this procedure allows the efficient recycling of the catalyst and the use of a wide variety of benzaldehyde derivatives, since electron-withdrawing and electron-donating groups are allowed. Interestingly enough, hydroxyl groups do not need any protection to provide the product of interest. The yields are moderate to excellent for reaction times ranging from 30 to 130 min.

The beneficial effect of the catalytic use of an ionic base, tetrabutylammonium hydroxide (TBAH), with respect to the more classical organic amine piperidine, was illustrated in the synthesis of pyridine-3,5-dicarbonitriles, *via* a MCR between malonitrile, thiophenol and various aldehydes. Both ionic<sup>53</sup> and nitrogenated<sup>54</sup> bases gave similar yields, but the use of TBAH in acetonitrile resulted in shorter reaction times.<sup>55</sup> As illustrated in Scheme 24, the desired heterocycles were obtained after only 1 h in refluxing acetonitrile in the presence of 50 mol% of TBAH, whereas 24 h were necessary in the presence of 30 mol% of piperidine in order to obtain similar yields.

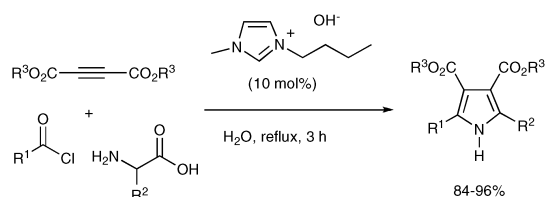
Finally, the [bmim]OH–H<sub>2</sub>O system has been used in the three-component condensation of acid chlorides with amino-acids and dialkyl acetylenedicarboxylates affording a one-pot access to highly functionalized pyrroles (Scheme 25).<sup>56</sup> The crucial role of the hydroxy counteranion of the IL catalyst was confirmed by comparison with the activity of the tetra-fluoroborate-containing IL analogue, which revealed to be a less effective catalyst. Thereby, this methodology constitutes an efficient eco-friendly alternative to more classical methods for the synthesis of pyrroles, such as the Hantzsch or the Paal–Knorr procedures.

## Ionic liquids as immobilizing liquid phase for MCRs

Solid supported synthesis introduced by Merrifield, widely used in combinatorial chemistry and high-throughput parallel synthesis, possess a lot of practical interest (no purification during the sequence, ease of isolation at the end of the synthesis). However, this technique presents limitations due to the heterogeneous reaction conditions. Low loading capacities, degradation of the polymers, longer reaction times, reduced reactive sites accessibility and difficult reaction monitoring are the main features making the solid supported chemistry not that appealing compared to homogeneous systems. Despite the reduced use of organic solvents for purification in polymer supported chemistry, large quantities of reagents are required to push the transformations to completion. Fluorous-phase synthesis, efficient for the separation of small molecules, presents the interest of being homogeneous reaction



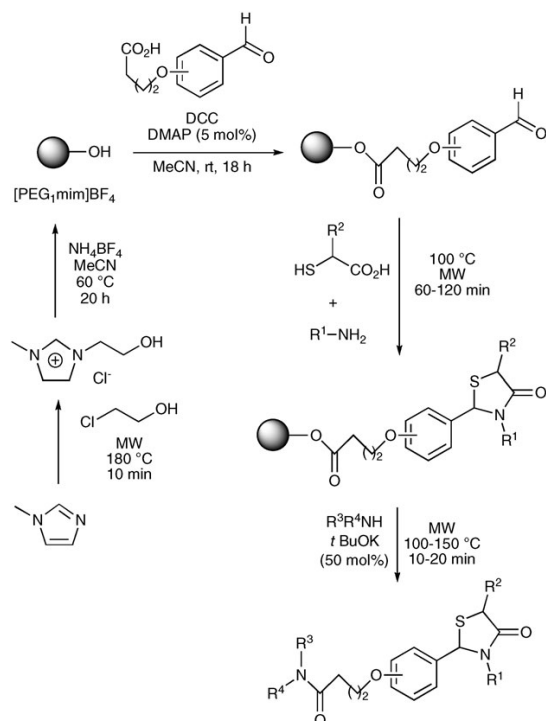
**Scheme 24** Basic ionic liquid-catalyzed multicomponent synthesis of pyridine-3,5-dicarbonitriles.



**Scheme 25** Use of the [bmim]OH–H<sub>2</sub>O system for the three-component synthesis of highly functionalized pyrroles.

conditions but limited development of the technique is certainly due to expensive perfluoroalkane solvents.

In the past decade, the concept of supported ionic liquid phase catalysis (SILPC) has gained much attention.<sup>57</sup> This methodology, which lies in the use of ionic liquids as the immobilizing agents, has emerged as an alternative to fluororous-phase synthesis in order to both enhance the benefits and diminish the negative aspects of solid supported chemistry. Green chemistry criteria are respected since the technique uses safe and reusable material. This technique has been employed for the first time for a bimolecular process in the Knoevenagel condensation and in 1,3-dipolar additions.<sup>58</sup> Subsequently, a synthetic application was reported with the one-pot three-component synthesis of a small library of 4-thiazolidinones from aldehydes, primary amines and mercapto acids (Scheme 26).<sup>59</sup> Upon immobilization of the aldehyde component on the PEG-derived ionic liquid support,<sup>60</sup> the multicomponent process occurs under solvent-free microwave irradiation with good conversions in less than 2 h. Cleavage of the product



**Scheme 26** Three-component synthesis of 4-thiazolidinones using SILPC methodology.

from the support is performed through amide formation promoted by primary or secondary amines and *t*-BuOK. The routine product isolation is rendered very simple thanks to the easy elimination of side product by washings from the IL-phase with an appropriate solvent. It is also important to note that SILPC allows easy monitoring of the reaction progress by standard analytical methods such as TLC or <sup>1</sup>H NMR.

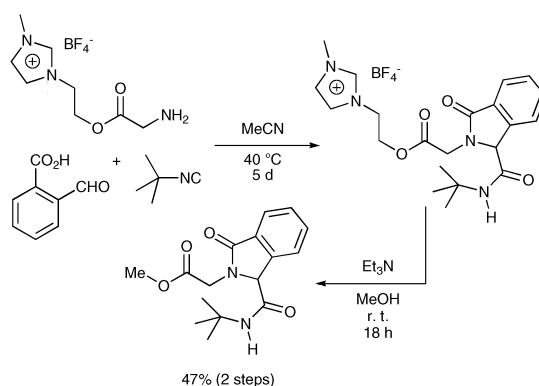
Isocyanides are compatible with the imidazolium ring present in some ionic liquid phases. Thereby, Ugi reactions may be run using the SILPC methodology. For example, condensation of *tert*-butyl isocyanide with phthalaldehydic acid and an ionic liquid-grafted amine in acetonitrile at 40 °C afforded after 5 days the corresponding Ugi product. Subsequent cleavage from the ionic support with triethylamine in methanol at room temperature afforded the final ester derivative in 47% overall yield (Scheme 27).<sup>61</sup>

Biginelli and Hantzsch reactions have also been performed using task-specific ionic liquid as a soluble support. Some aldehydes/ketones grafted on the ionic liquid phase were used as one of the multicomponent partners for the generation of DHPMs<sup>62</sup> and DHPs<sup>63</sup> grafted on the ionic liquid phase, respectively. The targeted heterocycles were easily cleaved from the support and isolated in good yields, making this strategy an efficient alternative to the classical homogeneous chemistry.

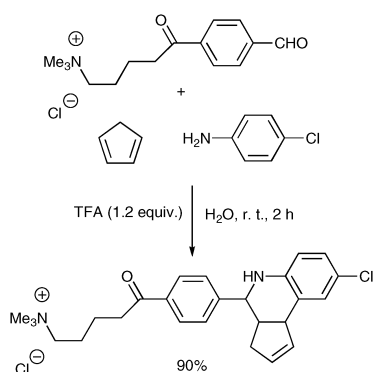
Finally, the group of Vaultier patented the use of onium salts for supported organic chemistry<sup>64,65</sup> and illustrated their potentialities in a Grieco's multicomponent reaction in water.<sup>66</sup> Indeed, they described a new three-component synthesis of quinolines from either supported benzaldehydes or supported anilines with equal efficiency, as illustrated with one example shown in Scheme 28.

## Control of stereochemistry in the course of MCRs in RTILs

The last part of this review discusses the challenging goal of stereocontrol in the combined use of MCRs and RTILs. Although the most famous MCRs such as Mannich, Hantzsch or Biginelli reactions are very “old” transformations, it is only



**Scheme 27** SILPC methodology applied to the Ugi reaction.



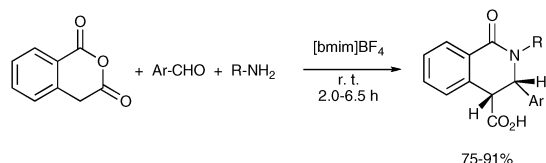
**Scheme 28** Grieco's three-component reaction with supported benzaldehydes and anilines.

recently that attention has been focused on the application of ILs as reaction media for asymmetric synthesis.

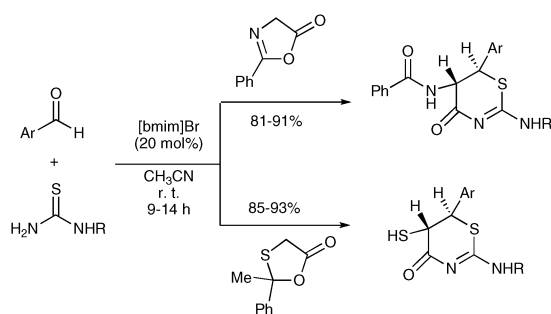
In 2003, Yadav *et al.* described the use of ionic liquids for a highly diastereoselective Biginelli-type synthesis of isoquinolic acid derivatives. Thus, condensation of benzaldehydes with anilines and homophthalic anhydride in [bmim]BF<sub>4</sub> at room temperature afforded the desired heterocycles in excellent yields and high *cis*-selectivity (Scheme 29).<sup>67</sup> Interestingly enough, when the same reactions were conducted in refluxing methanol, they afforded in longer reaction times and in lower yields the corresponding products as 3 : 1 mixtures of *cis*- and *trans*-isomers.

More recently, another diastereoselective ionic liquid-promoted three-component process has been reported for the synthesis of thiazinone derivatives, using masked amino- or mercapto acids (Scheme 30).<sup>68</sup> In this case, [bmim]Br was elected as the best catalyst used in acetonitrile, affording the expected heterocycles in very high *trans*-selectivity.

Recent progresses have been made in the development of chiral ionic liquids (CILs) or functionalized chiral ionic liquids (FCILs) as chiral promoters, and their applications in the field of asymmetric synthesis and catalysis have been compiled in some reviews.<sup>69,70</sup> However, up to now, there are few applications of CILs as effective reaction media or promoters for asymmetric MCRs.<sup>71</sup> The first enantioselective version of the transformation depicted in Scheme 30 was reported using L-prolinium sulfate (Pro<sub>2</sub>SO<sub>4</sub>) as chiral IL. Using either urea or thiourea derivatives, the desired products were obtained in good yields with enantiomeric excesses up to 94%.<sup>72</sup> However, to our knowledge, these results constitute the only example of a CIL-promoted enantioselective MCR for heterocyclic synthesis.



**Scheme 29** Ionic liquid-promoted diastereoselective multicomponent synthesis of *cis*-isoquinolic acid derivatives.



**Scheme 30** [bmim]Br-catalyzed multicomponent syntheses of *trans*-thiazinone derivatives.

## Conclusions

As illustrated through the selected studies reported in this review, the synergistic use of MCRs and RTILs allows the development of new methodologies for the efficient synthesis of heterocycles. Compared with conventional methods, these processes offer several advantages such as high yields, shorter reaction times, environmentally benign milder reactions, safe operations, simple work-up, efficient recovery and recycling of the IL. Thus, combining MCRs with RTILs opens an interesting eco-compatible alternative to more conventional approaches in the field of heterocyclic chemistry and should have an important impact in modern organic synthesis. To date, important achievements have been reached through the use of this approach, but efforts have now to be concentrated on the challenging control of the chirality by combining chiral ionic liquids and MCRs.

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