1. Introduction

In our group, we place a premium on the rapid access to a wide range of diverse small molecules. Our current focus spans the inhibition of dynamin GTPase, protein phosphatases 1 and 2A and the development of anti-cancer lead compounds.[1]-[10] While rapid access is paramount, we also strive to develop high levels of diversity in an environmentally friendly manner. That is, we are keen to apply the tenants of green chemistry at all stages of our drug development programs. To satisfy this need we have developed a particular interest in multicomponent reactions in benign solvents.

A multicomponent reaction (MCR) can be simply classified as a reaction in which three or more components are combined together in a single reaction vessel to produce a final product or products displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. Products from such MCRs result in high atom and step economy.

The first reported MCR was Strecker’s synthesis of racemic amino acids in the 1850’s.[11] Strecker’s amino acid synthesis combined an aldehyde, hydrogen cyanide and ammonia in a one pot procedure leading to a range of amino acids. With over 150 years history and development, MCRs have recently seen a resurgence, in part due to the ease of access to a wide range of diverse, highly functionalized molecules, in particular the synthesis of small heterocyclic rings of medicinal chemistry importance. A discourse on the physical properties of ionic liquids is out with the scope of this work. The chemistry, reactions and properties of ionic liquids has been addressed in a number of excellent review articles in this area.[12]-[20] In this chapter we describe the current state of play associated with MCRs in ionic liquids, with a focus on 3- and 4- component MCRs (3CRs and 4CRs respectively).[21]
For ease of discussion the application of MCRs in ionic liquids is broken down into the type of product generated: heterocyclic rings containing various numbers of heteroatoms and a classification of the reaction as either a 3CR or a 4CR.

2. Three component MCRs (3CRs)

2.1. Synthesis of acyclic products

MCRs are not only applicable to the synthesis of heterocyclic systems, but represent a very facile entry point to a range of acyclic compounds such as the amido substituted naphthols shown in Scheme 1. The treatment of β-naphthol with a wide range of aldehydes (aliphatic and aromatic), substituted amides in the presence of conventional ionic liquids (ILs), such as those based on the N-methyl, N-sulfonic acid imidazolonium [MSIM] cation, afforded rapid access to 1-amidoalkyl-2-naphthols and 1-amidoaryl-2-naphthols in good to excellent yields. In this area Zolfigol et al. have had particular success with the functionalised ILs such as [MSIM][Cl], [DSIM][Cl] and [MSIM][AlCl₄], under solvent-free conditions (Scheme 1).[22]

![Scheme 1. Synthesis of 1-amidoalkyl-2-naphthols: (i) [MSIM][Cl] or [DSIM][Cl] or [MSIM][AlCl₄], 120ºC, ~40 min.](image)

Hajipour et al. and Hervai et al. effected the same transformations, and extended the methodology to allow the use of urea as the amide source using a range of Bronstead acid based ILs (BAILs).[23],[24] Hajipor et al.’s approach used N-(4-sulfonic acid)butyltriethyl ammonium hydrogen sulfate [TEBSA][HSO₄], while Hervai et al. applied two BAILs: 3-methyl-1-(4-sulfonic acid)-butylimidazolium hydrogen sulfate [MIM-(CH₂)₃SO₃H][HSO₄] and N-(4-sulfonic acid)butylpyridinium hydrogen sulfate [Py-(CH₂)₃SO₃H][HSO₄] to effect the same transformations. [TEBSA][HSO₄] has been used previously as an efficient and reusable catalyst for nitration of aromatic compounds and esterification of various alcohols by different acids.[25]-[27] The acidic nature of BAILs has been exploited as catalysts for many other significant organic reactions, which proceed with excellent yields and selectivities and demonstrate the great potential of these ILs in catalytic technologies for chemical production.[23]

Kotadia et al. and Zhang independently reported the synthesis of similar 1-amidoalkynaphthols using solid supported ionic liquids (SSILs).[28] Kotadia used a benzimidazolium based...
ionic liquid immobilized on silica based solid support, while Zhang conducted the reaction in the presence of polyethylene glycol (PEG)-based dicationic acidic ionic liquid as a catalyst under solvent-free conditions.[29],[30] Supported reagents offer the advantages of simple and safe catalyst recycling.[28] All MCR-IL based approaches to 1-amidoalkynaphthols where highly substituent tolerant with excellent yields observed with both electron donating and electron withdrawing aldehydes.

Yadav and Rai reported a three component MCR approach to β-nitrocarbonitriles and β-nitrothiocyanates in [BMIM][OH] or [BMIM][BF₄]. The reaction proceeds via a Henry reaction to yield the β-nitrostyrenes followed by Michael addition of trimethylsilyl cyanide (TMSCN) or ammonium thiocyanate to yield the β-nitrocarbonitriles and β-nitrothiocyanates in modest overall yields of 53-58% (Scheme 2).[31],[32]

Scheme 2. Synthesis of β-nitrocarbonitriles and β-nitrothiocyanates: (i) [BMIM][OH] or [BMIM][BF₄], TMSCN, CH₃CN, 85-90ºC, 6-9h; (ii) [BMIM][OH] or [BMIM][BF₄], NH₄SCN, CH₃CN, 85-90ºC, 6-9h.

Zaho et al. has reported the combined Barbier / Friedel-Crafts alkylation of unsubstituted benzaldehydes with allylbromide and phenols to yield 4-(2-hydroxyphenyl)-4-phenylbut-1-enes promoted by BuPyCl/SnCl₂•2H₂O and their subsequent application to the synthesis of 4-(substituted phenyl)chromans (Scheme 3).[33]

Scheme 3. Synthesis of 4-(2-hydroxyphenyl)-4-substituted phenylbut-1-enes: (i) BuPyCl/SnCl₂•2H₂O.

The use of an enolisable ketone facilitated the synthesis of a family of β-amido ketones (Scheme 4). The reaction of an enolisable ketone, aryl aldehyde and acetonitrile or benzonitrile in the presence of TMSCl using a Bronsted-acidic ionic liquid 3-methyl-1-(4-sulfonic acid) butylimidazolium hydrogen sulfate [MIM-(CH₂)₄SO₃H][HSO₄] as catalyst gave a family of β-amido ketones in good yield.[34]
This enolisable ketone approach also allowed Fang et al. to conduct a three-component Mannich-type reaction (Scheme 5) with aromatic aldehydes, aromatic amines, and ketones catalyzed by a novel functionalized ionic liquid, 3-(N,N-dimethyldecylammonium)propanesulfonic acid hydrogen sulfate ([DDPA][HSO₄]) at room temperature to give various β-aminocarbonyl compounds in good yields.[35] [DDPA][HSO₄] was recycled and after six cycles, no loss in catalytic activity was reported. Gong et al. conducted the same reaction using cyclohexanone and [BMIM][OH] as the IL catalyst to afford the β-aminocarbonyl compounds in excellent yields.[36]

Liu et al. also explored the IL mediated Mannich reaction, but utilised a series task-specific ionic liquids in developing an asymmetric of β-aminoketones from isovaleraldehyde, methyl ketones, and aromatic amines in excellent yields (ca. 90%) and %ee's (~95%).[37] L-proline was used as the chiral catalyst (Scheme 6). The reaction with [DEMIm][BF₄], [DEEIm][BF₄], [BEIm][BF₄], [MEIm][BF₄] and [PEIm][BF₄] typically gave the desired product with an ee >95%. While the chemical yield dropped marginally on re-use from 96 to 85% over four cycles of IL use, the %ee remained constant.
Scheme 6. Catalysed asymmetric Mannich reaction: (i) task specific ionic liquid chosen from [DEIm][BF$_4$], [DEEIm][BF$_4$], [BEIm][BF$_4$], [MEIm][BF$_4$], and [PEIm][BF$_4$] / L-proline.

In a similar reaction sequence, Akbari and Heydari, replaced the activated ketone with trimethyl phosphite, in the presence of [MIM-(CH$_2$)$_4$SO$_3$H][CF$_3$SO$_3$], to affect rapid access to α-aminophosphonates (Scheme 7).[38] The reaction proceeded via protonation of the carbonyl moiety, imine formation and attack at the protonated imine by trimethylphosphite. The reaction was highly tolerant of substituents on the carbonyl containing compound with pyridyl, cinnamyl, etc., affording excellent yields of the corresponding α-aminophosphonates. The ionic liquid could be recycled with no observable loss of efficacy after six cycles.

Scheme 7. Synthesis of α-aminophosphonates: (i) [MIM-(CH$_2$)$_4$SO$_3$H][CF$_3$SO$_3$] (10 mol%), H$_2$O.

Reddy et al. also reported the synthesis of α-aminophosphonates via a three-component reaction of 5-amino-2,2-difluoro-1,3-benzodioxole, aromatic aldehydes, and diethylphosphite catalysed by silica-supported boron trifluoride (BF$_3$·SiO$_2$) in [BMIM][HCl] at room temperature (Scheme 8).[39] Yields were good to excellent and reaction times were typically 5 min versus 3h using conventional solvents.

Scheme 8. Synthesis of α-aminophosphonate catalysed: (i) BF$_3$·SiO$_2$ / [BMIM][HCl].

O-Protected cyanohydrins are versatile synthetic intermediates in organic synthesis for the preparation of a wide variety of substrates such as α-hydroxyacids, α-hydroxy ketones, α-amino acids, and β-amino alcohols.[40]-[43] Shen and Ji developed a mild synthesis of these key intermediates via the condensation of an aldehyde, trimethylsilyl cyanide (TMSCN), and Ac$_2$O in [BMIM][BF$_4$] (Scheme 9).[44] In addition, the recovered ionic liquid could be reused for subsequent runs without the loss of activity.
2.1.1. 3CRs yielding heterocycles with one ring nitrogen

Arguably the major utility of MCRs is in the synthesis of highly decorated heterocyclic compounds. In our group we are interested in the synthesis of heterocyclic scaffolds that can be used in medicinal chemistry programs to instill the correct level of biological activity. Davoodnia et al. reported an efficient procedure for preparation of 2,4,6-triarylpyridines by treatment of acetophenones, aryl aldehydes, and NH$_4$OAc in the presence of [MIM-(CH$_2$)$_4$SO$_3$H][HSO$_4$] (Scheme 10).[45] Aromatic aldehydes with both electron donating and electron withdrawing substituents were well tolerated.

In a related study, Heravi and Fakhr, reported a high yielding ultrasonic promoted synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives (Scheme 11), by the reaction of aryl aldehydes, thiols and malononitrile catalyzed by ZrOCl$_2$.8H$_2$O/NaNH$_2$ in [BMIM][BF$_4$] at room temperature.[46] Access to the same type of penta-substituted pyridines was also possible using [BMIM][OH] as described by Ranu (Scheme 11).[47]

The related 2,4,6-triaryl-1,4-dihydropyridines were generated in an Aldol-Michael-addition reaction cascade involving an aromatic aldehyde, acetophenone and NH$_4$OAc in [BMIM][BF$_4$] (Scheme 12).[48] The resulting 2,4,6-triaryl-1,4-dihydropyridines were then examined as potential catalysts for the the Diels-Alder reaction of $p$-quinone and cyclopentadiene, and maleic anhydride and cyclopentadiene.
Scheme 12. Synthesis of 2,4,6-triaryl-1,4-dihydropyridines: (i) [BMIM][BF₄], 80°C.

Wu used essentially the same reaction cascade described above, replacing acetophenone with acetoacetates which yielded, from [Bpy][BF₄], a series of 2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate esters (Scheme 13).[49] Compared with classical Hantzsch reaction conditions towards this type of product, this IL mediated reaction had the advantage of excellent yields, short reaction time, and easy workup.

Scheme 13. Synthesis of 1,4-dihydropyridines: (i) [BPy][BF₄], 100-110°C.

Quinolin-4(1H)ones constitute an important class of heterocyclic compounds because of their important pharmaceutical properties, such as anti-viral,[50],[51] anti-platelet,[52] and anti-tumor effects.[53] These compounds have been exploited as precursors for anti-cancer and anti-malarial agents.[54],[55] Yadav et al. described an efficient two step synthesis of quinolin-4(1H)ones, 5H-thiazolo[3,2-a]pyrimidine, and 4H-pyrimido[2,1-b]benzothiazoles at room temperature.[56] The initial reaction in the reaction was conducted with arylamine and Meldrum’s acid) and trimethylorthoformate in [BMIM][Br] at 40°C giving the corresponding arylaminomethylene-1,3-dioxane-4,6-diones. Cyclization occurred in [BMIM][BF₄] / OTf at 80°C under nitrogen to the quinolin-4(1H)ones in excellent yields (Scheme 14).[56]

Scheme 14. Synthesis of 4(1H)-quinolones: (i) [BMIM][Br], 40°C, N₂; (ii) [BMIM][BF₄]/OTf, 80°C.

Wang et al. reported a novel reaction of 2-(1-substitutedpiperidin-4-ylidene)malononitrile, benzaldehyde, and malononitrile or cyanoacetate in the synthesis of highly substituted isoquinoline derivatives (Scheme 15).[57] The three-component reaction of benzaldehyde, malononitrile, and ethyl 4-(dicyanomethylene)piperidine-1-carboxylate was reacted in [BMIM] [BF₄] at 50°C, delivering ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-arylisoquinol...
line-2(1H)-carboxylate derivatives being obtained in excellent yields. The highest yields were obtained with [BMIM][BF₄].

Scheme 15. Synthesis of ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2(1H)-carboxylate derivatives: (i) [BMIM][BF₄], 50°C.

There are many methods for the synthesis of acridine compounds containing 1,4-dihydropyridine moieties from aldehydes, dimedone, and anilines or ammonium acetates via heating in organic solvents, or catalysis by triethyl(benzyl)ammonium chloride (TEBAC) in water, or under microwave irradiation.[58] In a much more efficient approach, Li et al. utilised the three component MCR in [BMIM][BF₄] at room temperature of an aromatic aldehyde, 2-hydroxy-1,4-naphthoquinone and naphthalen-2-amine giving rise to a series of 14-aryl-1,6,7,14-tetrahydrodibenzo[a,i]-acridine-1,6-dione derivatives (Scheme 16).[59]

Scheme 16. Synthesis of 14-aryl-1,6,7,14-tetrahydrodibenzo[a,i]acridine-1,6-diones: (i) [BMIM][BF₄], rt.

Shi reported an efficient and green synthetic route to 3,3’-benzylidenebis(4-hydroxy-6-methylpyridin-2(1H)-ones) via condensation, addition and ammonolysis of an aldehyde, aniline and 6-methyl-4-hydroxypyran-2-one (Scheme 17).[60] Different solvents including [BMIM][Br], [BMIM][BF₄] and [BMIM][PF₆] were examined, with [BMIM][Br] giving the most favourable outcome (high yield and ease of product isolation).

Scheme 17. Synthesis of 3,3’-benzylidenebis(4-hydroxy-6-methylpyridin-2(1H)-ones): [BMIM][Br], 95°C.
2.1.2. 3CRs yielding heterocycles with two ring nitrogens

Pyrimidine derivatives are important biologically active heterocyclic compounds which possess antimalarial.[61] Gholap’s synthesis of 3,4-dihydropyrimidin-2-(1H)-ones from aromatic or aliphatic aldehydes with ethyl acetoacetate and urea (or thiourea), was promoted by ultrasound in [BMIM][BF₄] at room temperature affording the target compounds in excellent yields and short reaction times (Scheme 18).[62]

Scheme 18. Synthesis 3,4-dihydropyrimidin-2-(1H)-ones: (i) [BMIM][BF₄], 30ºC, ultrasound.

Similar pyrimidine analogues were accessed by Gui et al. through the use of acidic ionic liquids such as [MIM-CH₂COOH][HSO₄], [MIM-CH₂COOH][H₂PO₄], [MIM-(CH₂)₂COOH][HSO₄] and [MIM-(CH₂)₂COOH][H₂PO₄]) which successfully promoted the Biginelli coupling of an aldehyde, 1,3-dicarbonyl compound, and urea giving easy access to 3,4-dihydropyrimidin-2(1H)-ones.[63] Peng and Deng, used [BMIM][BF₄] and [BMIM][PF₆] as catalysts for the same Biginelli condensation reaction at 100ºC (Scheme 19).[64]

Scheme 19. The synthesis of 3,4-dihydropyrimidin-2-(1H)-ones: (i) IL chosen from [MIMCH₂COOH][HSO₄] or [MIMCH₂COOH][H₂PO₄] or [MIM(CH₂)₂COOH][HSO₄] or [MIM(CH₂)₂COOH][H₂PO₄], 75ºC.

Brønsted acidic ionic liquids have designed to replace solid acids and traditional mineral liquid acids like sulfuric acid and hydrochloric acid in chemical procedures.[65],[66] Using 3-carboxypyridinium hydrogensulfate [HCPy][HSO₄], 1,3-dicarbonyl compounds, aromatic aldehydes and urea or thiourea, Hajipour and Seddighi, successfully removed the traditional acid requirement in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Scheme 20).[67]

Scheme 20. Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones: (i) [HCPy][HSO₄], 120ºC.
Fang et al.’s dicationic acidic IL catalytic approach, in what amounted to a modified Biginelli approach, resulted in the synthesis of 3,4-dihydropyrimidin-2(1H)-one and 3,4-dihydropyrimidin-2(1H)-thione derivatives (Scheme 21), in good yields.[68] The products could be separated simply from the catalyst–water system, and the catalysts could be reused at least six times without noticeably reducing catalytic activity.

Scheme 21. Synthesis of 3,4-dihydropyrimidin-2(1H)-(thi)ones: (i) Dicationic acidic IL (shown in box), 90ºC.

Rather than use an acidic IL approach to dihydropyrimidinones (above) Mirzai and Valizadeh developed a microwave assisted Biginelli route using the weakly Lewis basic nitrite based ionic liquid, IL-ONO (Scheme 22).[69] These nitrite based Ils have also been used to carry out nitrosations of aromatic compounds in aqueous media.[70] Valizadeh, have reported the nitrozation of aromatic compounds using the same nitrite ionic liquid in aqueous media.[70]

Scheme 22. Synthesis of dihydropyrimidinones: (i) IL-ONO, MW, 80ºC.

Trisubstituted imidazoles can be rapidly accessed from a one-pot condensation of 1,2-diketone or α-hydroxyketone, aldehyde, and NH₄OAc in 1,1,3,3-N,N,N,N-tetramethylguanidinium trifluoroacetate (TMGT) at 100ºC (Scheme 23).[71] The synthesis of trisubstituted imidazoles in TMGT as promoter and solvent for the synthesis of trisubstituted imidazoles not only represented a dramatic improvement (15-40 min, 81-94%) over conventional thermal heating but the reaction times were comparable to the recently reported microwave irradiation (20 min in HOAc, 180–200ºC). There are related routes in a four-component approach (see section 2.2.3).

Scheme 23. Synthesis of trisubstituted imidazoles: (i) TMGT, 100ºC.
Khurana and Kumar have reported a simple and convenient synthesis of octahydroquinazolinone and biscoumarin derivatives (Scheme 24).\[72\] Despite prolonged heating (10 h) at 100ºC, the reaction of benzaldehyde, dimedone and urea in [BMIM][Br] gave only 30% of the expected product, 4,6,7,8-tetrahydro-7,7-dimethyl-4-phenyl-1H,3H-quinazoline-2,5-dione. Addition of TMSCl saw a reduction in reaction duration to 2.5 h wand a 92% isolated yield. Of the ILs examined [BMIM][Br] and [BMIM][BF₄] gave higher yields than [BMIM][Cl] and [BMIM][PF₆].

Scheme 24. Synthesis of octahydroquinazolinones: (i) [BMIM][Br], TMSCl, 100ºC.

Omprakash et al. used catalytic [BMIM][BF₄] and ultrasonics to obtain excellent yields of quinazolin-4(3H)ones from anthranilic acid, primary aromatic amine and carboxylic acids (Scheme 25). Of the anilines examined, only 4-nitroaniline required elevated temperature (50ºC), but this reaction was complete after 20 minutes.[73]

Scheme 25. Synthesis of 4(3H)-quinazolinones: (i) [BMIM][BF₄], ultrasound.

The related quinazoline nucleus has been prepared by Dabiri et al. from 2-aminobenzophenone derivatives, aldehydes and ammonium acetate in the presence of an protic ionic liquid, 1-methylimidazolium trifluoroacetate, [HMIM][TFA] (Scheme 26).[74]

Scheme 26. Synthesis of quinazoline derivatives: (i) [HMIM][TFA], 80ºC.

An analogous 6, 5-ring system, the 3-aminimidazo[1,2-α]pyridine, was accessed via condensation of an aldehyde, 2-aminazine and trimethylsilylcyanide, as an isocyanide equivalent under by simple heating in [BMIM][Br] in high yields with rather short reaction
Shaabani took a slightly different route to 3-arylsubstituted 3-aminoimidazo[1,2-a]pyridines using an isocyanide rather than an isocyanide equivalent. The use of substituted aminopyridines also allowed for the introduction of an additional C6 substituent.

![Scheme 27](image)

**Scheme 27.** Synthesis of 3-aminoimidazo[1,2-a]pyridines: (i) [BMIM][Br], 80ºC.

Using the Bronsted acidic ionic liquid triethylammonium hydrogen sulfate [TEBSA][HSO₄] Hajipour et al. synthesized pyrimidinone derivatives from a range of aromatic aldehydes, cyclopentanone, and urea or thiourea (Scheme 28).

![Scheme 28](image)

**Scheme 28.** Synthesis of 3-aminoimidazo[1,2-a]pyridines: (i) [BMIM][Br], 80ºC.

The reaction of phthalhydrazide, aromatic aldehydes, and malononitrile using controlled under microwave irradiation in the presence of [BMIM][OH] at an ambient temperature of 45ºC allowed facile access to 1H-pyrazolo[1,2-b]phthalazine-5,10-dione (Scheme 29).

![Scheme 29](image)

**Scheme 29.** Synthesis of pyrimidinone derivatives: (i) [TEBSA][HSO₄], 100ºC.

The reaction of phthalhydrazide, aromatic aldehydes, and malononitrile using controlled under microwave irradiation in the presence of [BMIM][OH] at an ambient temperature of 45ºC allowed facile access to 1H-pyrazolo[1,2-b]phthalazine-5,10-dione (Scheme 29).
Mixed solvent systems comprising [BMIM][BF₄], water and ethanol were used in the synthesis of 2H-indazolo[2,1-b]phthalazine-triones by condensation of phthalhydrazide, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds. Interestingly, the reaction required the addition of a catalytic quantity of sulfuric acid to effect the desired transformation (Scheme 30).[79]


2.1.3. 3CRs yielding heterocycles with three ring nitrogen atoms

While not strictly speaking the synthesis of a new ring system by MCR in ILs, Wang has exploited the MCR approach in an elegant synthesis of N-(α-alkoxyalkyl)benzotriazoles (Scheme 31) via the condensation of benzotriazole with various aldehydes and alcohols catalysed by acidic ionic liquid [HMIM][HSO₄] at room temperature.[80] The yield was up to 99%. Wang’s approach was effective when triethoxymethane was utilized instead of alcohols. Moreover, the [HMIM][HSO₄] was recyclable with no loss in catalytic activity.

Scheme 32. N-(α-alkoxyalkyl)benzotriazoles: (i) [HMIM][HSO₄], rt.

Pyrazolo[3,4-b]pyridines possess a wide range of biological activities such as psychotropic and cytotoxic, and are thus a very important scaffold in medicinal chemistry.[81],[82]

Scheme 33. Preparation of pyrazolo[3,4-b]pyridinone and pyrazolo[3,4-b]quinolinone derivatives: (i) [BMIM][BF₄], 80ºC.

Judicious choice of the 1,3-dicarbonyl source allows the synthesis of either pyrazolo[3,4-b]pyridinone derivatives or pyrazolo[3,4-b]quinolinone (Scheme 32). The combination of an
aldehyde, 5-amino-3-methyl-1-phenylpyrazole, and Meldrum’s acid in [BMIM][BF₄] affords the pyrazolo[3,4-b]pyridinone, while the use of dimedone affords the pyrazolo[3,4-b]quinolones.[83]

Zhang showed that the 1,3-dicarbonyl source was not limited to Meldrum’s acid or dimedone derivatives with the introduction of 1H-indene-1,3(2H)-dione for a mild synthesis of indeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one derivatives in excellent yields (Scheme 33).[84]

\[
\text{Scheme 34. Synthesise indeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one: (i) [BMIM][Br], 95ºC.}
\]

Zhang et al. reported the reaction of aldehydes, 5-amino-3-methyl-1-phenylpyrazole and malononitrile or ethyl cyanoacetate in [BMIM][BF₄] as a green route to pyrazolo[3,4-b]pyridines (Scheme 34).[84]

\[
\text{Scheme 35. Preparation of pyrazolo[3,4-b]pyridine derivatives: (i) [BMIM][BF₄], 80ºC.}
\]

Yao et al. synthesised 4-aryl-3,4-dihydro-1H-pyrimido[1,2-a]benzimidazol-2-one via the reaction of aryl aldehyde, 1,3-dicarbonyl compounds and 1H-benzo[d]imidazol-2-amine in [BMIM][BF₄] (Scheme 35).[85] The reaction accomplished in [BMIM][BF₄] exhibited higher yield (75%) than other counterparts.

\[
\text{Scheme 36. Synthesis of 4-aryl-3,4-dihydro-1H-pyrimido[1,2-a]benzimidazol-2-one: (i) [BMIM][BF₄], 90ºC.}
\]

Wang has a particular interest in the development novel methods for the preparation of various biologically important heterocyclic compounds by using ionic liquids. This group uses ILs as both novel reaction media and reaction promoters.[86],[87] Shi et al. also have similar interest and this led to the synthesis indeno[2,1:5,6]pyrido[2,3-d]pyrimidine and pyrimido[4,5-b]quinoline derivatives from aromatic aldehydes, 6-amino-3-substituted-1-methyl-
pyrimidine-2,4(1H,3H)-diones and dimidone analogues derivatives in ionic liquid without any catalyst (Scheme 36).[88]

**Scheme 37.** Synthesis of 5-aryl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione: [BMIM][Br], 95°C.

Pyrimidoquinolinedione derivatives are known to possess antitumor, anticancer, antihypertensive, antibacterial activity and are Kaposi’s sarcoma-associated herpesvirus and topoisomerase inhibitors.[89],[90] Entry to this highly biologically active scaffolds can be obtained by the reaction of aldehydes, 1-naphthylamine and barbituric acid in [BMIM][BF₄] gave 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones (Scheme 37). While the reaction proceeded in traditional organic solvent, yield enhancements and shorter reaction times were evident with the use of [BMIM][BF₄].[91]

**Scheme 38.** The synthetic of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones: (i) [BMIM] [BF₄], 90°C.

### 2.1.4. 3CRs yielding heterocycles with three ring nitrogens

The purine bioisosteres, [1,2,4]triazolo[1,5-a]pyrimidine, have been reported to possess antitumour activity.[92] Using both [BMIM][BF₄] and [Bpy][BF₄] as reaction solvents, Li synthesised 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]-triazolo[1,5-a]pyrimidine derivatives from aldehydes, 3-amino-1,2,4-triazole and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione yielding 4-, 5- and 7- substituted derivatives (Scheme 38). The 5- and 7- positions are known to be important for retention of antitumour activity.[93]

**Scheme 39.** Synthesis of 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]triazolo[1,5-a]pyrimidine derivatives: (i) BMIM [BF₄] or [byp][BF₄].
2.1.5. 3CRs yielding heterocycles with one ring oxygen

The synthesis of heterocyclic compounds with oxygen in the ring is slightly more complex, only due to the reduced numbers of suitable oxygen nucleophiles to affect the final ring-closing step. The 4\(H\)-pyran core is found in a wide range of natural products and it has thus attracted a considerable degree of attention.[94]-[96] The high reactivity of 4\(H\)-pyran derivatives has led to their use as synthons in the synthesis of more complex species. Access to highly substituted 4\(H\)-pyrans is easily accomplished by the 1,1,3,3-tetramethylguanidine catalysed addition of aromatic aldehydes, malononitriles, and \(\beta\)-dicarbonyl in [BMIM][BF\(_4\)] (Scheme 39).[97]

Scheme 40. Synthesis of 4\(H\)-pyran derivatives: (i) TMG, [BMIM][BF\(_4\)], 80ºC.

With dimedone as the 1,3-dicarbonyl source the corresponding 5-oxo-5,6,7,8-tetrahydro-4\(H\)-benzo[\(b\)]pyran derivatives were accessed in [BMIM][BF\(_4\)], [HMIM][BF\(_4\)], [OMIM][BF\(_4\)], [OMIM][PF\(_6\)] and [DMIM][PF\(_6\)]. In this instance no additional catalyst was required and the reactions were complete in 2-6 h with yields ranging from 52% to 98%. [98] Fang et al. reported a subtle variation leading to the synthesis of more highly substituted 5-oxo-5,6,7,8-tetrahydro-4\(H\)-benzo[\(b\)]pyrans by condensation of aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and dimedone (or 1,3-cyclo-hexanedione) in water catalyzed by acidic ionic liquids such as [TEBSA][HSO\(_4\)], [TBPSA][HSO\(_4\)], [EDPSA][HSO\(_4\)] (Scheme 40).[99] The reactions gave the products in good yields between 86 to 94%.

Scheme 41. Synthesis of 5-oxo-5,6,7,8-tetrahydro-4\(H\)-benzo[\(b\)]pyrans: (i) Ionic liquid chosen from [TEBSA][HSO\(_4\)], [TBPSA][HSO\(_4\)] and [EDPSA][HSO\(_4\)].

Interest in oxygen containing heterocycles is not limited to those with biological activity. A number of analogues, such as the 2-amino-2-chromenes are natural products that have found utility in cosmetics and pigments. They also have a role as biodegradable agrochemicals.[100]-[102] Traditional approaches to this scaffold required the reaction of aldehydes, active methylene containing compounds and activated phenols. Stoichiometric quantities of organic base (piperidine) in volatile organic solvents are also required.[103],[104] By replacing the organic solvent with [BMIM][OH] the reaction proceeded with aromatic aldehydes,
malononitrile with α- or β-naphthol in the absence of additional catalyst (Scheme 41).[105] After five reuses of the [BMIM][OH] the isolated product yield had dropped from 91% to 85%, which may be due to [BMIM][OH] degradation.

![Scheme 42. Synthesis of 2-amino-2-chromenes: (i) [BMIM][OH], H₂O, reflux.](image)

The basic 4H-pyran scaffold can be increased in complexity by modification of the basic building blocks described above, e.g. in Schemes 39 and 41. Both Khurana and Magoo, and Zakeri reported the synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones by the reaction of β-naphthol, aromatic aldehydes, and dimedone derivatives (Scheme 42).[106],[107] Smooth conversion was accomplished through the use of catalytic p-TSA in [BMIM][BF₄] at 80°C for 35-45 min. The [BMIM][BF₄] could be recycled without a reduction in product yield.

![Scheme 43. Synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones: (i) [BMIM][BF₄], p-TSA or BAIL, 120°C.](image)

Zheng and Li accessed the tetrahydrobenzo[b]pyran and pyrano[c]chromene scaffolds via a series of novel Lewis basic task-specific ionic liquids. These novel IILs were used to catalyse the addition of aromatic aldehydes, dimedone and malononitrile can also be used as catalysts in multicomponent reaction access during the mixture of tetrahydrobenzo[b]pyran and pyrano[c]chromene derivatives (Scheme 43).[108]

![Scheme 44. Synthesis of tetrahydrobenzo[b]pyran and pyrano[c]chromene derivatives: (i) [TETA][TFA] (5%), H₂O-EtOH (1:1), reflux.](image)
2.1.6. 3CRs yielding heterocycles with two ring oxygen atoms

Dihydropyrano[3,2-c]chromene-3-carbonitriles are important heterocycles with a wide range of biological properties.[109]-[111] A number of 2-amino-4Hpyrans are reported to be useful photoactive materials.[112] The task specific ionic liquid, hydroxyethanolammonium acetate [HEAA], was used to initiate a domino cascade of 4-hydroxycoumarin, aldehydes, and malononitrile at room temperature ultimately yielding 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives (Scheme 44).[113]

![Scheme 45. Synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives: (i) [HEAA], pulverise, rt.](image)

Gong et al. reported facile method for the synthesis of 4H-pyrans in the presence of basic ionic liquid [BMIM][OH] as catalyst in aqueous medium (Scheme 45).[114] The synthesis of 2-amino-4-aryl-5-oxo-4H,5H-pyrano[3,2-c]chromence-3-carbonitrile was achieved by the three-component condensation of an aromatic aldehyde, malononitrile with 4-hydroxycoumarin in the presence of 10 mol% [BMIM][OH] at 100°C.

![Scheme 46. Synthesis of 2-amino-4-aryl-3-cyano-5-oxo-4H,5H-pyrano[3,2-c]chromenes: (i) [BMIM][OH], H$_2$O, 100°C.](image)

The 3,4-dihydro-2H-furo[3,2-c]coumarin core is present in a number of natural products ranging including Novobiocin and warfarin. Earlier methods to this core include the oxidative cyclisation of the Michael adduct from the reaction of cyclic 1,3-diketones and chalcones using a phase transfer catalyst; from 1,3-dicarbonyl compounds and (E)-β-bromo-β-nitrostyrenes in the presence of tert-butylammonium bromide (TBAB) (20 mol %);[115]-[117] and the manganese acetate promoted radical cyclization of 4-hydroxycoumarin and 2-hydroxy-1,4-naphthoquinone with electron-rich alkenes.[118] Rajesh et al. reported a much simpler and greener approach for regio- and diastereo-selective synthesis of furocoumarins (Scheme 46).[119] These reactions proceeded chemo-, regio- and stereoselectively and furnished compounds in good to excellent yields (81-92%).
Coumarin derivatives have received considerable attention because they possess several types of pharmacological properties, such as antibacterial, anticancer. The coumarins have attracted the attention of a number of research groups interested not only in their biological activity, but also in developing more activity, but also in developing more environmentally friendly approaches to their synthesis. Gong et al. reported the condensation of 4-hydroxycoumarin, aldehydes, and Meldrum’s acids or malononitrile or α-cyanocinnammonitriles in the presence of [BMIM][OH]. While Chen et al. used 4-hydroxycoumarin, benzaldehyde and 1,3-dicarbonyl by use 1,3-dimethyl-2-oxoimidazolidine-1,3-diium cation [DMDBSI][2HSO₄] were employed as the model reactions in the presence of different catalysts (Scheme 47). Both approaches offered ease of access and considerable improvements over the traditional approaches to this class of compounds.

Thiophenes, dihydrothiophenes and tetrahydrothiophenes are known important constituents of a range of pharmacologically active compounds. While these compounds are of significant interest to medicinal and synthetic chemists, the synthetic routes to highly functionalised sulfur heterocycles are not well developed. Notwithstanding this, Zhang et al. have reported the synthesis of thiopyrans from aldehydes, malononitrile and cyanothioacetamide in an ionic liquid [BMIM][BF₄] as a recyclable solvent and promoter without the need of a catalyst (Scheme 48).

Thiopyrans, dihydrothiophenes and tetrahydrothiophenes are known important constituents of a range of pharmacologically active compounds. While these compounds are of significant interest to medicinal and synthetic chemists, the synthetic routes to highly functionalised sulfur heterocycles are not well developed. Notwithstanding this, Zhang et al. have reported the synthesis of thiopyrans from aldehydes, malononitrile and cyanothioacetamide in an ionic liquid [BMIM][BF₄] as a recyclable solvent and promoter without the need of a catalyst (Scheme 48).
Given that most of the synthetic procedures towards sulfur heterocycles suffer from some drawbacks such as low yields, long reaction times, the requirement for harsh reaction conditions, it is not surprising that a number of groups have risen to the challenge and examined the use of ionic liquids as a potential method for enhancing the reaction outcomes whilst increasing the efficiency of the synthesis. Kumar et al. have developed a series of novel amino acid derived functional ionic liquids that facilitated the synthesis of dihydrothiophene and tarcine derivatives in good yield under mild conditions from 2-arylidenemalononitrile, 1,3-thiazolidinedione, aliphatic or aromatic amines were added with ionic liquid [Bz-His(n-propyl)₂-OMe][Br] and water (Scheme 49). While the products were shown as single diastereoisomers, no details of the level of diastereoselectivity were provided.

Scheme 50. Synthesis of dihydrothiophenes: (i) [Bz-His(n-propyl)₂-OMe][Br], 70°C.

2.1.8. 3CRs yielding heterocycles with ring oxygen and nitrogen atoms

The synthesis of simple heterocycles with a single type of heteroatom is important, but a considerable number of biologically active compounds have different types of heteroatom within a single structure. The benzo[b][1,4]oxazin scaffold as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. Benzo[b][1,4]oxazin derivatives have been used as the basic framework for substances of interest in numerous therapeutic areas, such as anti-Candida albicans agents, antifungals, and kinase inhibitors. Ebrahim et al. used [BMIM][Br] as both the solvent and reaction promoter for the room temperature three-component condensation of 2-aminophenol, an aldehyde and isocyanide to prepare benzo[b][1,4]oxazines (Scheme 50).

Scheme 51. Synthesis of benzo[b][1,4]oxazines: (i) [BMIM][Br], rt.

Asri et al. described use of ionic liquids as complementary new media for multicomponent reactions leading to the 2,6-diazabicyclo[2.2.2]octane core (Scheme 51). Interestingly both hydrophobic and hydrophillic Ils [BMIM][BF₄] and [BMIM][NTf₂] gave acceptable yields, as the original synthesis required the use of toluene and a significant excess of molecular sives to remove water and drive the reaction forward. The original synthesis of these
2,6-diazabicyclo[2.2.2]octanes required 6 g of molecular sieves per 200 mg reagent. Thus the use of ILS represents a significant greening of this synthesis.[141]

![Scheme 52](image_url)

**Scheme 52.** Synthesis 2,6-diazabicyclo[2.2.2]octane core: (i) [BMIM][BF$_4$] or [BMIM][NTf$_2$], 110ºC, 4 Å sieves.

The synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles was first reported by Otto in 1974.[142] These molecules have since been shown to possess interesting biological activity.[143] Balaskar et al. simplified the synthesis of this important class of compounds in a triethylammonium acetate [TEAA] ionic liquid catalyzed reaction of aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one at room temperature (Scheme 52). TEAA plays dual role as reaction media and catalyst. These reactions are rapid, complete in 25 min, and typically high yielding (>90%).[144]

![Scheme 53](image_url)

**Scheme 53.** Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4 dihydropyrano[2,3-c]pyrazoles: (i) [TEAA], rt.

The furopyridine core is another privileged scaffold in medicinal chemistry.[145],[146] Shi et al. rectified what they perceived as an oversight in this area with their synthesis of the furopyridine motifs by reaction of an aldehyde, 5-amino-3-methyl-1-phenylpyrazole and tetronic acid. They explored the use of [BMIM][Br], [BMIM][BF$_4$], [PMIM][Br], water, glacial acetic acid, acetone, and ethanol as potential solvents for the synthesis of furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one derivatives (Scheme 53).[147] Across the range of aromatic aldehydes examined, the ILS [BMIM][Br], [BMIM][BF$_4$], and [PMIM][Br] consistently gave the highest product yields and the shortest reaction times.

![Scheme 54](image_url)

**Scheme 54.** Synthesise the furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one derivatives: (i) ILS, 95ºC.
Moghaddam reported the synthesis of novel spiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]tetraone derivatives by the combination of isatin, barbituric acid, and cyclohexane-1,3-dione derivatives in the presence of alum (KAl(SO$_4$)$_2$•12H$_2$O) as a catalyst for 15 min and [BMIM][PF$_6$] (Scheme 54).[148] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets.[149]

![Scheme 55. Synthesis of spiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]tetraone derivatives: (i) [BMIM][PF$_6$], alum, 100ºC.](image)

The synthesis of furopyrimidines and 2-aminofurans have received little attention with only a few procedures reported. Among these, the furo[2,3-d]pyrimidines have been shown to possess sedative, antihistamine, diuretic, muscle relaxant, and antiulcer properties.[150]-[156] The condensation of an aldehyde, N,N-dimethylbarbituric acid and alkyl or aryl isocyanide in [BMIM][Br] gave furo[2,3-d]pyrimidine-2,4(1H,3H)-diones in high yields at room temperature within 20 minutes (Scheme 55).[157]

![Scheme 56. Synthesis of furo[2,3-d]pyrimidine-2,4(1H,3H)-diones: (i) [BMIM][Br], rt, 15-20 min.](image)

The potential antitumour pharmacophore, benzopyrano[2,3-d]pyrimidine,[158] was accessed by Gupta et al. by the condensation of the salicyladehyde, malononitrile, and dimethylamine at room temperature in [BMIM][BF$_4$] at room temperature (Scheme 56). However, this approach was limited to the use of dimethlamine, with the diethylamine resulted in no reaction.[159]

![Scheme 57. Synthesis of benzopyranopyrimidines: (i) [BMIM][BF$_4$], rt.](image)
2.1.9. 3CRs yielding heterocycles with ring sulfur and nitrogen atoms

4-Thiazolidinones have been exploited as potential bactericidal, antifungal, anticonvulsant, anti-HIV, and antitubercularotic agents.[160],[161] While there have been multiple synthetic approaches, there is still considerable scope to develop a more environmentally friendly and efficient approach to this scaffold.[162],[163] Lingampalle et al. have developed a rapid entry to 4-thiazolidinones via the N-methylpyridinium tosylate [NMP][Ts] cyclocondensation of amines, aromatic ketones, and mercaptoacetic acid.[164],[165] The reaction proceeds via imine formation, followed by rapid cyclocondensation at 120 ºC (Scheme 57).

![Scheme 58. Synthesis of 4-thiazolidinones: (i) [NMP][Ts], 120ºC, 3h.](image)

The (1H)-quinolones, thiazolo[3,2-a]pyrimidines and pyrimido[2,1-b]benzothiazoles display considerable bioactivity and are important lead compounds in the development of anti-viral, anti-platelet, anti-cancer and anti-malarial agents.[166]-[168] While there are many reported synthesis of pyrimido[2,1-b]benzothiazoles, arguably Yadav et al.’s 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMim][TFA] mediated MCR is the most direct and efficient reported thus far (Scheme 58).[169]

![Scheme 59. Synthesis of 2,3-diaryl/2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones: (i) [MOEMim][TFA].](image)

2.1.10. 3CRs yielding heterocycles with ring oxygen, sulfur and nitrogen atoms

Application of a tandem Knoevenagel, Michael and ring transformation reactions involving 3-arylrhodanines, aromatic aldehydes and a mercaptacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one, in a chiral ionic liquid L-prolinium sulfate [Pro₂SO₄], gave 6-mercaptopyranothiazoles with diastereoselectivities of 88-95%ee (Scheme 59).[170] The reactions were conducted at room temperature 25-30 h, followed by isolation to yield a single diastereomer in 76-90% yields.
Scheme 60. Synthesis of 2-methyl-2-phenyl-1,3-oxathiolan-5-one: (i) [Pro$_2$SO$_4$], rt.

The biologically important $4H$-benzo[b]pyrans can be smoothly accessed as shown in Scheme 60 in excellent yields (77-95%) after stirring for 30-50 min at ethanol reflux. In this instance [BMIM][OH] was used as a catalyst.[121]

Scheme 61. Benzo[b]pyrans: (i) [BMIM][OH], EtOH, reflux.

2.2. 4CRs yielding heterocycles

2.2.1. 4CRs yielding heterocycles with one nitrogen in the ring

Increasing the number of components in MCRs from three to four offers the potential to increase substituent diversity, atom and step economy. This increased structural complexity allows for a facile access to highly decorated scaffolds, but interestingly in the four component IL mediated MCR, this has been limited to the synthesis of heterocyclic compounds. For example, rapid access to both alkyl and aromatic substituted 1,4-dihydropyridine derivatives can be accomplished via the reaction of an aldehyde, a 1,3-dicarbonyl compound, Meldrum’s acid and ammonium acetate as the nitrogen source in [BMIM][BF$_4$] (Scheme 61).[172],[173]

Scheme 62. Synthesis of 1, 4-dihydropyridine derivatives: (i) [BMIM][BF$_4$].

2.2.2. 4CRs yielding heterocycles with ring oxygen and nitrogen atoms

Kanakarajuwe et al. have exploited the four-component MCR for the synthesis of novel antibacterial chromeno[2,3-$d$]pyrimidin-8-amines in [BMIM][BF$_4$] (Scheme 62). Simple
stirring of a mixture of α-naphthol, malononitrile, aryl aldehydes and NH₄Cl in [BMIM] [BF₄] and with trace triethylamine (TEA) in DMF allowed direct isolation of the desired analogue, bypassing the more traditional route which involved isolation of corresponding iminochromenes.[174]

Scheme 63. General synthetic route of chromeno[2,3-d]pyrimidine-8-amine derivatives: (i) [BMIM][BF₄], TEA/DMF; (ii) NH₄Cl, 100°C.

2.2.3. 4CRs yielding heterocycles with two ring nitrogens

The biological roles of substituted imidazoles are well documented and numerous biologically active analogues have been reported.[175] Shaterian et al. have developed both a three and four component MCR route from benzil (or benzoin), substituted benzaldehydes and ammonium acetate (3-component), or with the addition of phenyl hydrazine (4-component) for the synthesis of 2,4,5-trisubstitutedimidazoles and 1,2,4,5-tetrasubstituted imidazoles respectively.[176] N-Methyl-2-pyrrolidonium hydrogen sulfate [NMP][HSO₄] at 100ºC was found to be superior to all previous reports which used a wide variety of catalys to conduct the same transformations. Recyling of the [NMP][HSO₄] saw a gradual diminution of the product yield from 98% to 82% over seven cycles. While this team examined the four component route (addition of phenylhydazine) giving 1,2,4,5-substituted imidazoles in high yields using Brønsted acidic ionic liquid, [NMP][HSO₄] (Scheme 63).

Scheme 64. Synthesis of 2,4,5- and 1,2,4,5-substituted imidazoles by a three or four component MCR: (i) [NMP][HSO₄].

Pyrano[2,3-c]pyrazoles represent an important scaffold in medicinal chemistry with multiple synthetic approaches developed. These approaches include synthesis in water, ethanol reflux, microwave assisted and solvent free aporaches. Each approach comes replete with its own set of advantages and disadvantages from excess solvent requirements, long reaction times and poor yields.[177]-[180] Khurana et al. synthesis of 4H-pyrano[2,3-c]pyrazoles
avoids most of these disadvantages by providing for a high yielding (typically >85%), short duration cyclocondensation of hydrazine monohydrate or phenyl hydrazine, ethyl acetooacetate, aldehydes, and malononitrile in [BMIM][BF₄] with catalytic quantities of L-proline (10 mol%) (Scheme 64).[181]

![Scheme 65. Synthesis of pyrano[2,3-c]pyrazoles: (i) [BMIM][BF₄], L-proline (10 mol%), 50°C.](image)

Xiao et al. have described a novel, efficient, and green procedure for the synthesis of 3-(5-amino-3-methyl-1H-pyrazol-4-yl)-3-arylpropanoic acid derivatives through the four-component reaction in [BMIM][BF₄] (Scheme 65).[182] Reactions were rapid (5 min) and the product isolated by pouring onto water and recrystallisation from EtOH / H₂O to afford pure product.

![Scheme 66. Synthesis of 3-(5-amino-3-methyl-1H-pyrazol-4-yl)-3-arylpropanoic acid derivatives: (i) [BMIM][BF₄].](image)

2.2.4. 4CRs yielding heterocycles with >three ring nitrogens

Ghahremanzadeh et al. reported the green synthesis of 1H-indolo[2,3-b]pyrazolo[4,3-e]pyridines from indolin-2-one, 3-oxo-3-phenylpropanenitrile, phenylhydrazine and benzaldehyde under a variety of conditions (Scheme 63).[183] The best reaction outcome was observed with the use of p-TSA in [BMIM][Br] at 140°C (Scheme 66).

![Scheme 67. Synthesis of 1H-indolo[2,3-b]pyrazolo[4,3-e]pyridines: (i) [BMIM][Br], p-TSA, 140°C.](image)

Building on their earlier report on the synthesis of spiro[indolinepyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine]triones from barbituric acid, phenylhydrazine, 3-oxo-3-phenylpropanenitrile and isatin, Ghahremanzadeh et al. noted that the use of mixture of alum
(KAl(SO$_4$)$_2$·12H$_2$O) and [BMIM][PF$_6$] was a green approach to the same class of compounds (Scheme 67).[184],[185]


3. Conclusions

In this brief review we have demonstrated the considerable utility of room temperature ionic liquids in multicomponent reactions. Almost universally, the addition of an ionic liquid increases the speed of reaction and reaction yields. In many cases the ionic liquid was used as both the solvent and the reaction promotor. It was possible to add catalytic quantities of ionic liquids in conventional solvent and still achieve a much greener reaction outcome.

While the linear variant of the four-component MCR in ionic liquids is currently poorly described, there is little doubt that room temperature ionic liquids will aid in the synthesis of such species. Overall the IL-MCR approach is an extremely useful one, especially for the rapid entry to highly functionalised heterocyclic molecules of potentials use in medicinal chemistry.

Author details

Ahmed Al Otaibi and Adam McCluskey

Chemistry, School of Environmental & Life Sciences, The University of Newcastle, University Drive, Callaghan NSW, Australia

References


[52] Huang, L. J.; Hsich, M. C.; Teng, C. M.; Lee, K. H.; Kno, S. C. Synthesis and Antipla-
et Activity of Phenyl Quinolones. Bioorganic & Medicinal Chemistry 1998;6
1657-1662.

[53] Gasparotto, V.; Castagliuolo, I.; Chiarelotto, G.; Pezzi, V.; Montanaro, D.; Brun, P.;
Palu, G.; Viola, G.; Ferlin, M. G. Synthesis and Biological Activity of 7-Phenyl-6,9-di-
hydro-3H-pyrrolo[3,2-f]quinolin-9-ones: A New Class of Antimitotic Agents Devoid

F.; LaVoie, E. J. 5H-Dibenzo[c,h]1,6-naphthyridin-6-ones: Novel Topoisomerase I-Tar-
geting Anticancer Agents With Potent Cytotoxic Activity. Bioorganic & Medicinal
Chemistry 2003;11 2061-2073.

[55] Theeraladanon, C.; Arisawa, M.; Nishidi, A.; Nakagawa, M. A Novel Synthesis of
Substituted Quinolines Using Ring-closing Metathesis (RCM): its Application to the
Synthesis of Key Intermediates for Anti-malarial Agents. Tetrahedron 2004;60
3017-3035.

[56] Yadav, A. K.; Sharma, G. R.; Dhakad, P.; Yadav, T. A Novel Ionic Liquid Mediated
Synthesis of 4(1H)-Quinolones, 5H-thiazolo[3,2-a]pyrimidin-5-one and 4H-pyrimi-

[57] Wang, X. S.; Wu, J. R.; Li, Q.; Zhang, M. M. A Novel and Green Method for the Syn-
thesis of Highly Substituted Isoquinoline Derivatives in Ionic Liquid. Journal of Heter-
ocyclic Chemistry 2009;46 1355-1363.

[58] Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Mora, A.; Suárez, M.; Ochoa, E.; Mo-
rales, A.; Del Bosque, J. R. Synthesis and Conformational Study of Acridine Deriva-
tives Related to 1,4-dihydropyridines. Journal of Heterocyclic Chemistry 1995;51
235-238.

[59] Li, Y.; Xu, X.; Shi, D.; Ji, S. One-pot Synthesis of 14-Aryl-1,6,7,14-tetrahydrodibenzo-
[a,i]acridine-1,6-dione in Ionic Liquids. Chinese Journal of Chemistry 2009;27
1510-1514.

bis(4-hydroxy-6-methylpyridin-2(1H)-one) Derivatives through Multi-Component

[61] Agarwal, A.; Srinivas, K.; Puri, S. K.; Chauhan, P. M. S. Synthesis of 2,4,6-trisubstitut-
4645-4650.

Promoted Novel and Efficient One-pot Synthesis of 3,4-dihydropyrimidin-2-(1H)-
one at Ambient Temperature Under Ultrasound Irradiation. Green Chemistry
2004;6 147-150.


[71] Shaabani, A.; Rahmati, A. 1,1,3,3-N,N,N,N-Tetramethylguanidinium Trifluoroacetate Ionic Liquid–Promoted Efficient One-Pot Synthesis of Trisubstituted Imidazoles. Synthetic Communications 2006;36 65-70.


[86] Zhang, X.; Fan, X.; Niu, H.; Wang, J. An Ionic Liquid as A Recyclable Medium for the Green Preparation of * * * -bis (substituted benzylidene)Cycloalkanones Catalyzed by FeCl3 6H2O. Green Chemistry 2003;5 267-269.


[137] Macchiariulo, A.; Costantino, G.; Fringuelli, F.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. 1,4-Benzothiazine and 1,4-Benzoxazine Imidazole Derivatives with Antifungal Activity: A Docking Study. Bioorganic & Medicinal Chemistry 2002;10 3415-3423.


[144] Balaskar, R. S.; Gavade, S. N.; Mane, M. S.; Shingate, B. B.; Shingare, M. S.; Mane, D. V. Greener Approach Towards the Facile Synthesis of 1,4-dihydropyran[2,3-c]pyrazol-5-yl Cyanide Derivatives at Room Temperature. Chinese Chemical Letters 2010;21 1175-1179.


