Organic Chemistry in Ionic Liquids Using Non-Thermal Energy-Transfer Processes

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Abstract: As a result of the chemical industry being under pressure to reduce its usage of volatile solvents ionic liquids are of considerable interest as environmentally benign solvents for organic synthesis programs. Isolation of products is generally facilitated by the fact that ionic liquids form biphasic systems with many organic product mixtures. Recent research has emphasised the use of ionic liquids as solvents and co-solvents in reaction conditions requiring non-thermal heating processes since their ionic nature makes them susceptible to interaction with electromagnetic fields (heating by microwave irradiation). Furthermore, their low vapour pressure allows high temperatures to be reached and leads to interesting behaviour during ultrasound promoted reactions.

Keywords: Ionic liquids, microwave, ultrasound, synthesis.

INTRODUCTION

From rather humble beginnings as electrolytes, the use of ionic liquids as environmentally benign solvents for organic synthesis has become a very topical area of research (for an excellent historical overview see [1f]). They have turned from being laboratory curiosities into commercially available products which find broad use in many research groups all over the world (Figure **1**). Ionic liquids consist of organic cations with appropriate anions and are liquids with melting points at or close to room temperature. With vanishingly small vapour pressures and the capacity to dissolve a wide range of organic and inorganic substrates, ionic liquids are promising substitutes for volatile organic solvents. Important properties of ionic liquids include the potential for recycling and their compatibility with various organic compounds and organometallic catalysts. In addition, the products from reactions conducted in ionic liquids can be extracted easily using various organic solvents. Volatile products can be simply distilled directly from the solutions. Also the ability to tune reaction conditions by choosing the appropriate counter ion gives them added importance (for example [bmim][PF_6] is extremely hydrophobic, whereas [bmim][BF_4] is a hydrophilic ionic liquid). These versatile materials have been widely used in place of traditional solvents in a variety of organic reactions, and recent developments have been ably reviewed emphasising the applications in catalysis [1].

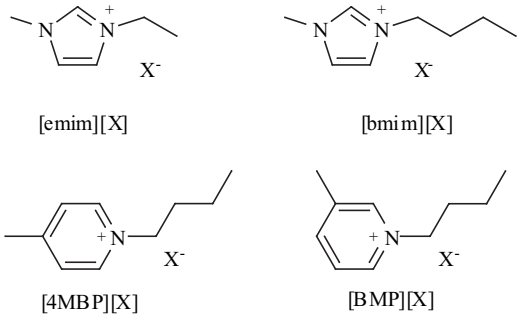

Fig. (1). Examples for commercially available ionic liquids.

A new area has opened up over the past five years in the application of ionic liquids in microwave and ultrasound-assisted reactions. While ionic liquids were initially used in minimal quantities to dope classical solvents, thus rendering the solution more susceptible to interaction with an electromagnetic field, more recent research has used them directly as solvent for the reaction.

Microwaves are being defined as the electromagnetic waveband between radio waves and infrared, thus having a frequency range between 300 MHz and 300 GHz. The so-called ISM-frequencies (*Industrial Scientific Medical*) assigned by the FCC cover the range of 2.4 – 2.5 GHz to avoid interference with other applications (airborne, airport and marine radar, missile guidance, weather radar etc.). The application of microwaves in chemistry generally relies on the effect of the dielectric heating process. The energy transfer is governed by two principal mechanisms. Heat is generated by the dipole rotation when a reaction medium or a reactant with a high dielectric constant (ε) tries to align itself to the oscillating field of the microwave. In addition, the electric field of the microwave generates ionic conduction also resulting in rapid heating.

While the early reports describe the (not unproblematic, if not dangerous) use of commercial household microwave ovens to carry out the reactions, later research makes use of more sophisticated instruments which have been specially designed for synthetic chemistry thus allowing the precise control of the reaction parameters[‡].

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[‡]For information on commercial laboratory microwave equipment allowing control of mixing, temperature, pressure and output power etc. consult the manufacturers sites, e.g.: http://www.cem.com; http://www.milestonesci.com or http://www.personal-chemistry.com.

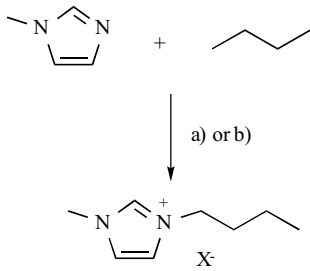
1570-193X/05 $50.00+.00

In contrast to the electromagnetic microwaves, ultrasound is the transmission of mechanical waves with frequencies between 15/20 kHz and 10 GHz. The application of ultrasound in organic chemistry has become fairly standard over the years and has been shown on many occasions to enhance reactions rate as well as improve yields. In various cases reactions could be carried out which otherwise required harsher reaction conditions, like high temperature or high pressure. The effect of ultrasound on liquids is based on a cavitational process forming small bubbles. The immediate acoustic collapse of these bubbles liberates a considerable amount of energy in short time, leading to local temperatures reportedly up to 5000 °C and pressures of up to a couple of 100 bars, the surrounding liquid itself remaining unaffected. The application of ultrasound in ionic liquids changes the cavitation characteristics to a great extent as these liquids have no vapour pressure. For these reasons, even less volatile substrates can undergo cavitational activation. Most reports on the use of ultrasound in conjunction with ionic liquids describe the utilisation of simple and inexpensive ultrasound cleaning baths.

PREPARATION OF IONIC LIQUIDS USING MICROWAVE IRRADIATION

The first report on the microwave-assisted preparation of ionic liquids dates back to the year 2000 when a patent application, which was filed the year before by Personal Chemistry AB, became public knowledge [2]. The inventors described a process of irradiating *N*-methyl imidazole with an alkyl halide in ethyl acetate (Scheme **1a**).

Later Varma reported on the solvent-free preparation of [amim]-type ionic liquids using a microwave oven as an irradiating source [3, 4]. The equipment used was a common household microwave oven equipped with inverter technology. According to the authors this is the only way to effectively adjust and control the output power of a household microwave oven. The preparation of ionic liquids has also been carried out by irradiating equimolar amounts of *N*-methyl imidazole and an alkylating agent (like 1-bromo butane) in open glass vessels. In some cases the amount of alkylating agent had to be increased to two equivalents. Upon microwave irradiation, the ionic liquid formed increased the polarity of the reaction medium thereby increasing the rate of microwave absorption (Scheme **1b**).

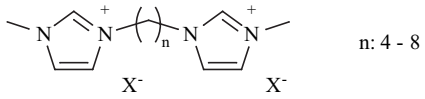


a) X = Cl; EtOAc; μw; 170 °C; 5 min; no yield given.
b) X = Br; μw; 240 W; 75 s; 86%.

Scheme 1. Preparation of [bmim] derivatives.

In both cases, the reaction times compared to the classical processes could be shortened dramatically. However, it should be noted, that several groups have commented on the shortcomings of these routes owing to the excessive use of alkylating agents and their irreproducibility [7, 8].

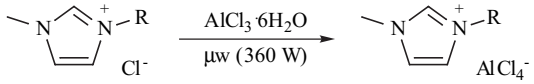
Expanding this earlier work, Varma and Namboodiri reported on the solvent-free preparation of dicationic ionic liquids (Figure **2**) which have become of recent interest owing to their electrical conducting capabilities.



X = Cl, Br, I

Fig. (2). Dicationic ionic liquid.

Subsequently, their interest in room temperature ionic liquids led them to describe the preparation of [amim]-type ionic liquids bearing the tetrachloroaluminate counter ion (Scheme **2**) [5].

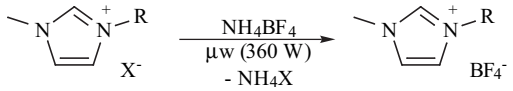


R: *n*-butyl, *n*-hexyl, *n*-octyl

Scheme 2. Preparation of [amim][$AlCl_4$] using microwave.

This work has been recently criticised by Seddon who noted that the presence of water of crystallisation would lead to the hydrolysis of the tetrachloroaluminate resulting in the formation of hydroxoaluminate species [9]. The aluminate ionic liquids have been used as efficient solvent-catalysts for the protection and deprotection of alcohols as tetrahydropyranyl ethers and for Friedel-Crafts reactions.

Continuing efforts to improve their synthesis and also the thermal stability of ionic liquids led to the solvent-free preparation of [amim]-type ionic liquids bearing the tetrafluoroborate counter ion [6]. Unfortunately, some acetone was needed to facilitate the separation from ammonium salts produced as by-products (Scheme **3**). Nevertheless, the authors were able to show that these ionic liquids are thermally stable up to 350 °C.



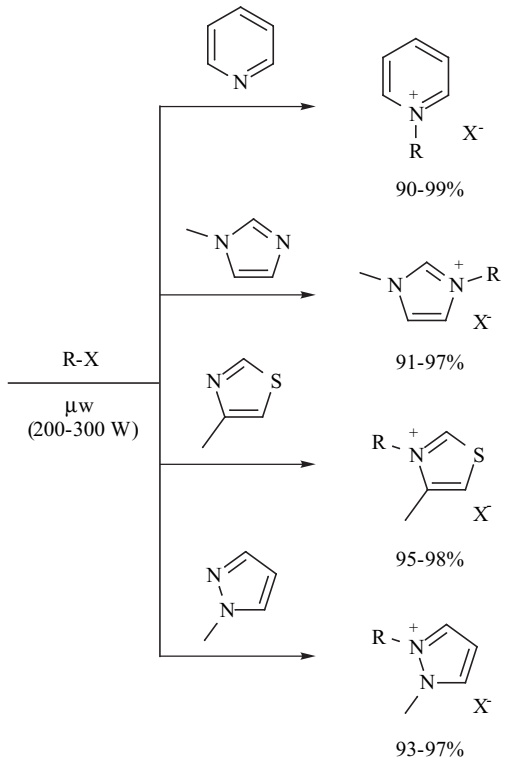
R: *n*-butyl, *n*-hexyl, *n*-octyl
X: Cl, Br, I

Scheme 3. Preparation of [amim][BF_4] using microwave.

In an attempt to improve the solvent-free preparation of ionic liquids, others have reported an improved approach whereby the reaction temperature was moderated by placement of the reaction vessel in a water bath [7]. Since a medium to large excess of alkylating agent was required this process is not ideal.

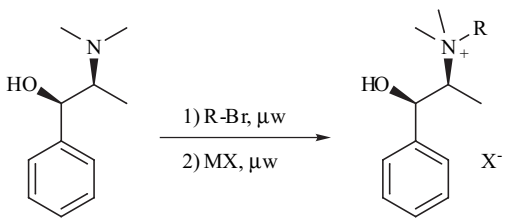
Rebeiro and later Seddon overcame these problems by carrying out the alkylation reaction in sealed vessels [8, 9]. Seddon described a process using a commercial multimode microwave reactor and apart from the classical [amim]-derivatives his report also describes the preparation of *N*-alkylpyridinium-, *N*-alkyl-3-methylthiazolium- and *N*-alkyl-2-methyl- pyrazolium-based ionic liquids (Scheme **4**). The

reaction times for the latter two series were significantly longer than those observed for the [amim]-series.



Scheme 4. Preparation of ionic liquids by Seddon *et al.*

The synthesis of chiral ionic liquids has also been achieved [10]. Starting from (-)-*N*-methylephedrine the researchers were able to develop an efficient one-pot procedure (both possibilities, one-pot-three-component and one-pot-two-step were shown to work) for the preparation of a range of (1*R*,2*S*)-ephedrine-based ionic liquids which they intended to investigate as media for asymmetric synthesis and catalysis (Scheme **5**).



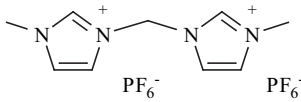
Scheme 5. Preparation of chiral ionic liquids.

PREPARATION OF IONIC LIQUIDS USING ULTRASONICATION

In 2002 Lévêque described the use of an ultrasound promoted preparation of ionic liquids [11]. The publication was later followed by a PCT patent publication [12]. The syntheses of [bmim][BF_4] and [bmim][PF_6] starting from [bmim][Cl] were compared. The anion exchange reactions were carried out in heterogeneous phase both under normal conditions (magnetic stirring) and under ultrasonic irradiation. Progress of the reactions was followed by conductivity measurements. The results show, that while under normal conditions the reactions are complete after about 30 hours, the ultrasonicated reactions are finished within one hour. The authors draw the conclusion that this drastic reduction in reaction time is due to the reduction in particle size since the bulk reaction temperature was maintained by a cryostat.

APPLICATION OF IONIC LIQUIDS UNDER MICROWAVE CONDITIONS

The thermal behaviour of ionic liquids under microwave irradiation has been intensely studied. Leadbeater *et al.* investigated the ionic liquid mediated heating of nonpolar solvents [13]. They were able to show that classical solvents like hexane, toluene, tetrahydrofuran and dioxane could be heated in closed vessels far above their normal boiling points when doped with an ionic liquid, a method which had been first suggested by Ley [17]. It could be further shown that the choice of the ionic liquid is crucial to avoid contamination of the reaction mixture by decomposition products. The best results were observed with the dicationic liquid (***1***) shown in Figure **3**, which has the slight disadvantage, in that it is a high melting ionic liquid (Table **1**).



(***1***)

Fig. (3). Dicationic liquid devised by Leadbeater *et al.*

Table 1. Microwave heating of doped solvents (heating time 120 s)

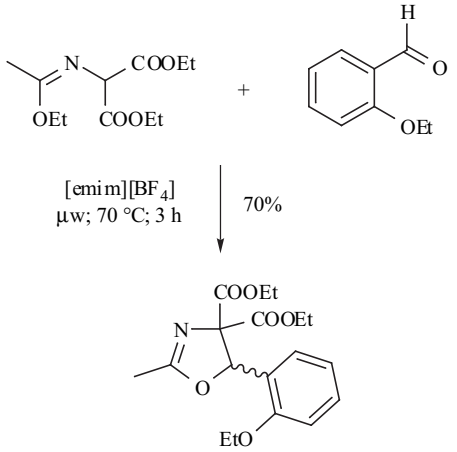
solvent	*T* attained (°C)	*T* w/o ionic liquid (°C)	normal *bp* (°C)
hexane	300	46	69
toluene	291	109	111
THF	181	112	66
dioxane	233	76	101

Others have investigated the thermal stability of ionic liquids based on 1-*n*-butyl-3-methylimidazolium salts ([bmim$^+$][X$^-$]) using thermo gravimetric analysis [14]. All of the ionic liquids examined exhibited similar thermal stability regardless of the counter anion and decomposed drastically in the temperature range 380 – 400 °C. The heating rates under microwave irradiation could be shown to be largely affected by the counter anion, with the triflate showing the fastest rate, reaching 200 °C in about 120 seconds.

Along similar lines work by Ondruschka used a range of [bmim]-derivatives and investigated the microwave power dependent heating characteristics [15]. The results show that the curvature of the heating curve increases with decreasing

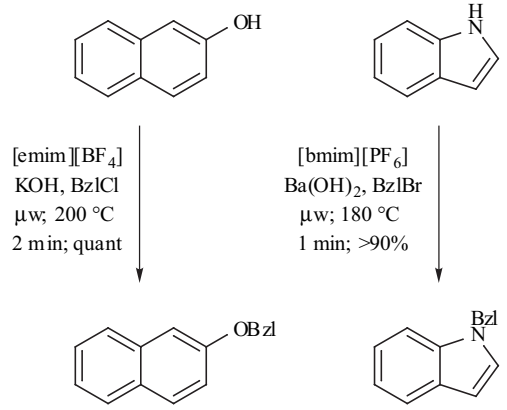
microwave power. In other words, any increase in microwave power results in a drastic decrease in heating time. The heating time itself does not show a linear behaviour for a constant increase of microwave power due to the dependency of the absorbed microwave power on the square of the electrical field strength. The authors concluded that it is necessary to determine the optimal power input for every ionic liquid in order to reduce heating time in an energy-favourable way.

The first description of an organic reaction being carried out in a microwave-irradiated ionic liquid solution dates back to the year 2000, when Bazureau investigated in a brief study 1,3-dipolar cycloadditions [16]. When reacting an imidate of diethylamino malonate with 2-ethoxybenz-aldehyde they noted a distinct increase in reaction rate when adding [emim][BF_4] to the reaction mixture. The reaction time could be shortened further when subjecting the mixture to microwave irradiation (Scheme **6**). Interestingly, microwave irradiation did not exhibit any beneficial effect on the isolated yield which is often the case.



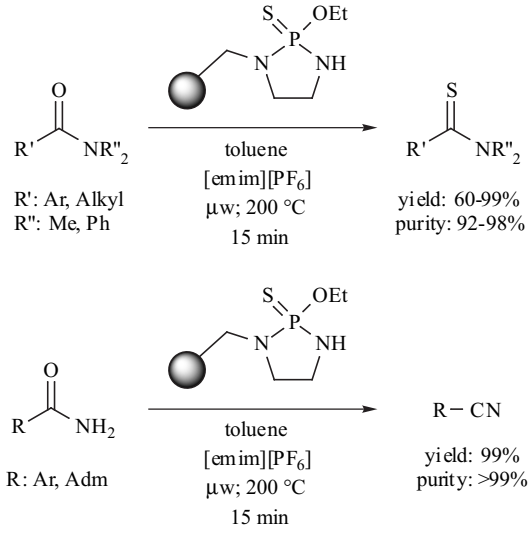
Scheme 6. 1,3-Dipolar cycloaddition reactions.

Later a patent application from Personal Chemistry described microwave-assisted alkylation reactions in ionic liquids like [emim][BF_4] or [bmim][PF_6] [2]. The reactions were carried out at temperatures between 160 and 200 °C. Yields were reported to be generally high and reaction times ranged from 1 to 3 minutes (Scheme **7**).



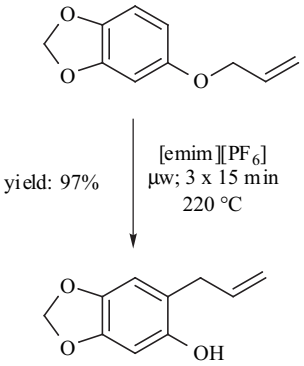
Scheme 7. Alkylation reactions.

The Ley group described the first use of ionic liquids and microwave heating in reactions with polymer-supported reagents [17]. Considerable rate enhancements were observed when converting amides into thioamides using a newly devised polymer-supported thionating reagent (Scheme **8**). The reactions, which were carried out with microwave heating in a sealed tube at 200 °C, displayed a marked acceleration and proceeded much cleaner, when the solvent (toluene) was doped with about 5% of [emim][PF_6].



Scheme 8. Polymer-supported thionation/dehydration.

A recent synthesis of the natural product carpanone based on polymer-supported reagents reported by the same group included a Claisen rearrangement as one of the early steps [18]. The reaction proceeded smoothly in high conversion and the product was easily isolated by a simple filtration through a plug of silica (Scheme **9**).

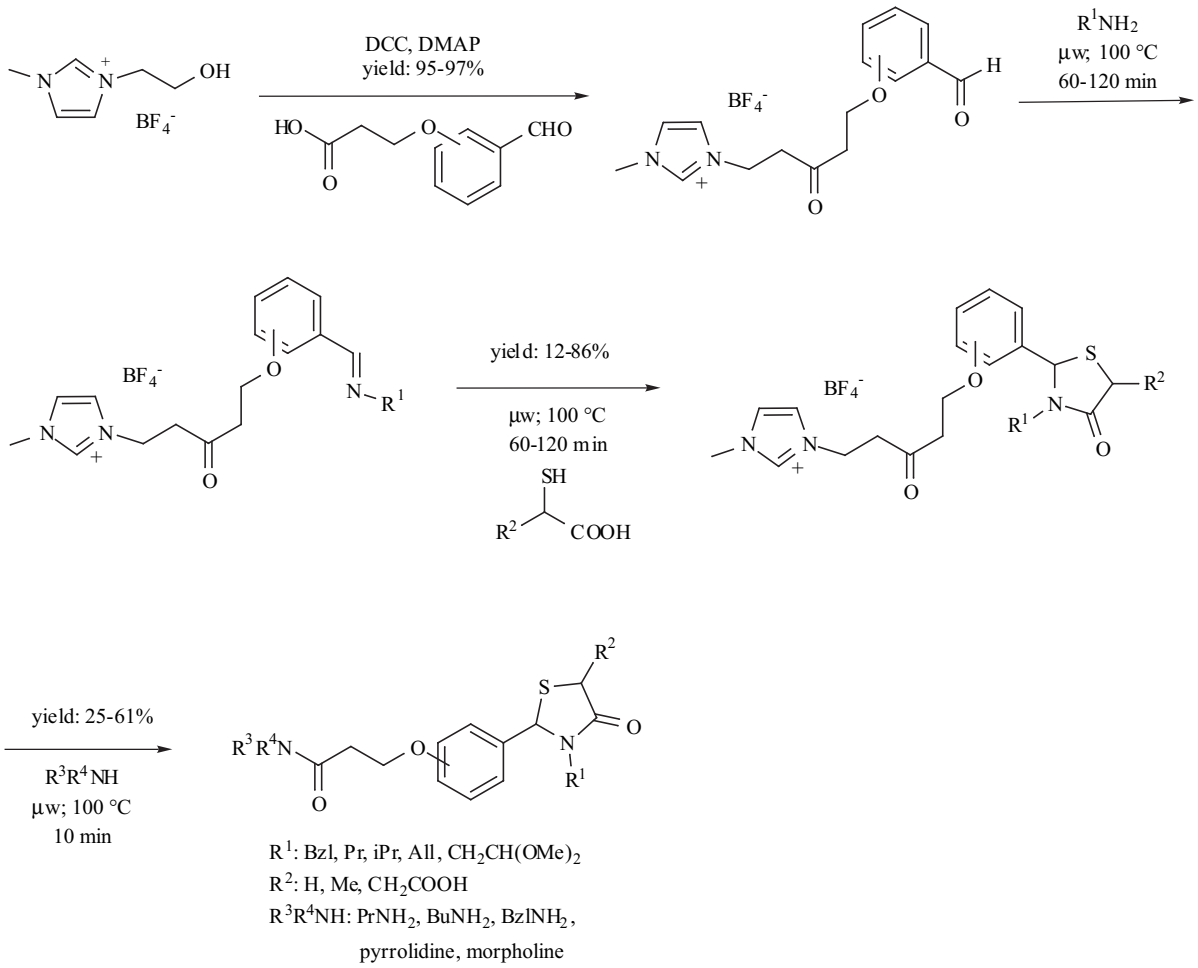


Scheme 9. Claisen rearrangement.

Introducing grafted ionic liquids Bazureau prepared a hydroxylated [emim]-derivative, which was then loaded *via* esterification with a substrate [19]. In a first implementation of this method the authors reported a Knoevenagel condensation and on the synthesis of an imidazoline (Figure **4**).

Recently, a preparation of a small library of 4-thiazolidinones (Scheme **10**), presenting a multistep preparation using a sequence of microwave reactions was also reported [20].

Similarly the preparation of 2-thioxotetra-hydropyrimidine-4-(1*H*)-ones has been described involving



Scheme 10. Grafted ionic liquid-phase supported synthesis.

microwave promoted ring formation and cleavage from the ionic liquid carrier molecule (Scheme **11**) [21].

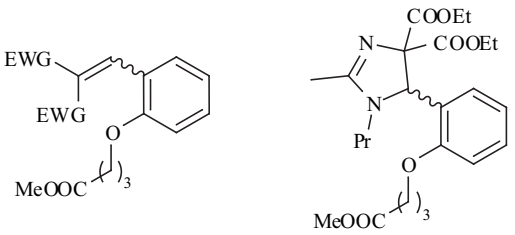
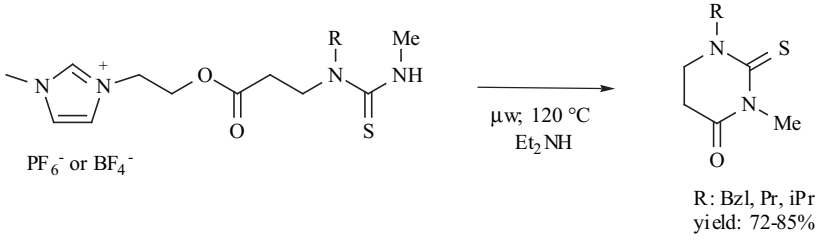


Fig. (4). Compounds generated by Knoevenagel condensation and 1,3-dipolar cycloaddition after cleavage.

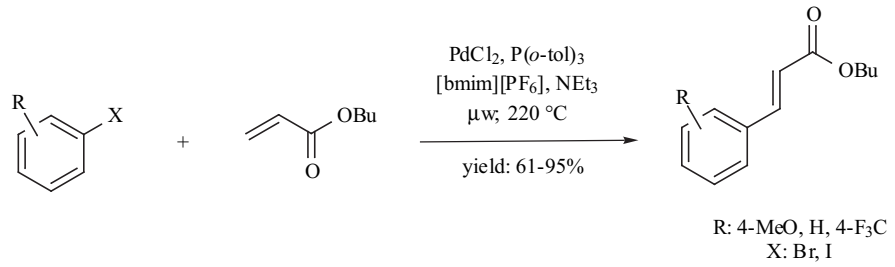
Heck arylation reactions in [bmim][PF_6] under microwave irradiation are also possible [22]. The couplings were performed in sealed tubes at 220 °C with palladium dichloride in the presence of tri-*o*-tolylphosphine (Scheme **12**). The reaction products were isolated by distillation in good to excellent yield and in a follow-up work the researchers were able to extend the chemistry to the less reactive aryl chlorides using Fu's catalyst generated *in situ* from Herrmann's palladacycle and [(*t*Bu)$_3$PH]BF_4 [23].

Later, She and Pan described a similar process using a ligand-free system with palladium on charcoal as catalyst [24]. The results were comparable to those obtained above.

The microwave-assisted synthesis of pinacol boronates from aryl chlorides has been achieved in the presence of a catalyst formed *in situ* from palladium(II) acetate and an imidazolium chloride [25]. While the latter was supposed to act as a ligand for the palladium, it might serve as a dielectric heating agent, although the authors did not



Scheme 11. Preparation of 2-thioxotetrahydropyrimidine-4-(1*H*)-ones.



Scheme 12. Microwave-assisted Heck reaction.

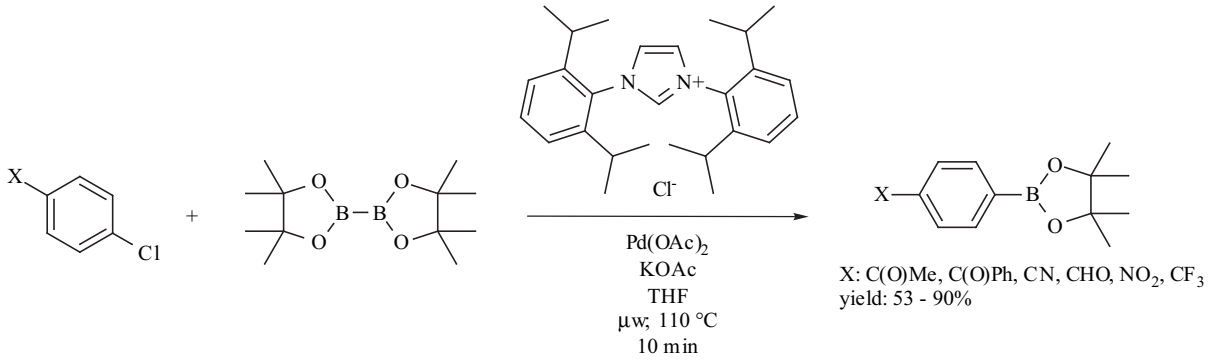
comment on that (Scheme **13**). Compared with classical heating, a significant acceleration of the reaction was observed.

Kappe investigated microwave-promoted hetero-Diels-Alder reactions in ionic liquid doped solvents [26]. In the course of this research, a series of functionalised 2(1*H*)-pyrazinones were subjected to microwave heating in sealed tubes. The azadiene system readily underwent a cycloaddition reaction with an intramolecular dienophile (Scheme **14a**). The bicyclic products were obtained in moderate to good yields. The products of a Diels-Alder-retro-Diels-Alder reaction sequence could be generated by using acetylenic dienophiles (Scheme **14b**).

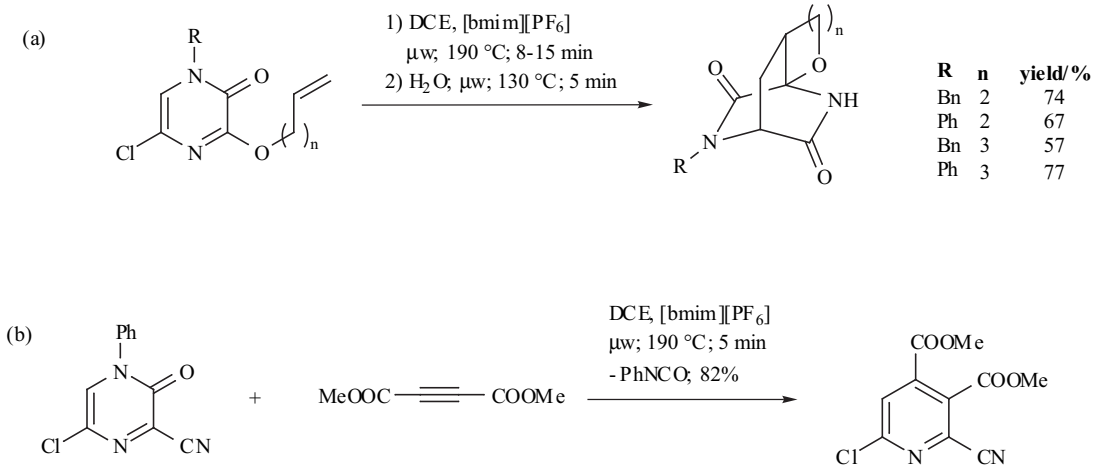
While trying to carry out a related process with ethene they observed a rapid pressure-build up due to an ionic liquid-initiated polymerisation reaction which led to the destruction of the reaction vessel.

Leadbeater was able to show that ionic liquids can be successfully employed to dope organic solvents to facilitate microwave-assisted Diels-Alder reactions [13]. Reacting methyl acrylate with 2,3-dimethyl butadiene at 200 °C allowed shortening of the reaction time to five minutes, thus offering a significant rate enhancement over the classical reaction conditions (Scheme **15**).

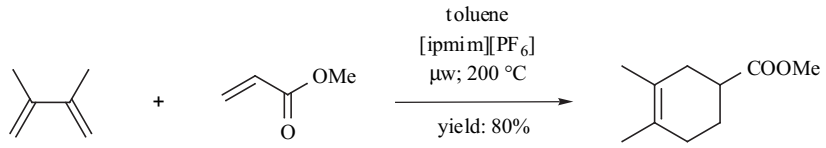
The Michael addition of imidazole to methyl acrylate also proceeds smoothly [13]. Here the ionic liquid is only acting as a heating agent without becoming chemically involved in the reaction. The product could be obtained after two minutes of reaction time in a good isolated yield, and again showed improvement over previously reported methods (Scheme **16**).



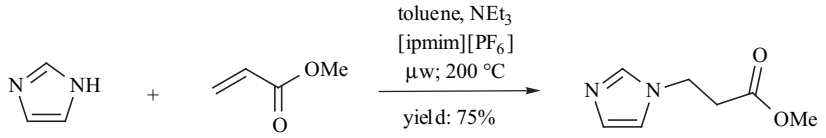
Scheme 13. Borylation of aryl chlorides.



Scheme 14. Hetero Diels-Alder reaction.



Scheme 15. Diels-Alder reaction.



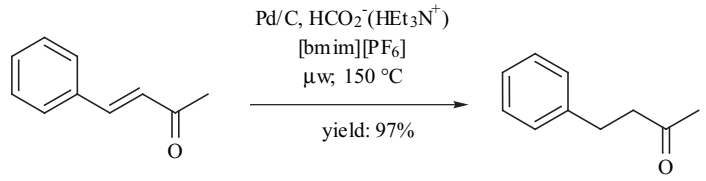
Scheme 16. Michael addition.

Catalytic transfer hydrogenation is also possible in ionic liquids [27]. Triethylammonium formate was used as the hydrogen source and was found to be superior to ammonium formate. Various functional groups (nitro, alkene, alkyne) were reduced to give essentially pure products which could be isolated in good yield by liquid-liquid extraction. The authors were able to show that the catalyst/ionic liquid system could be recycled although a notable loss in activity was observed over subsequent runs (Scheme **17**). The attempted reductive de-halogenation of haloarenes was however unsuccessful, since the halide liberated caused the decomposition of the ionic liquid.

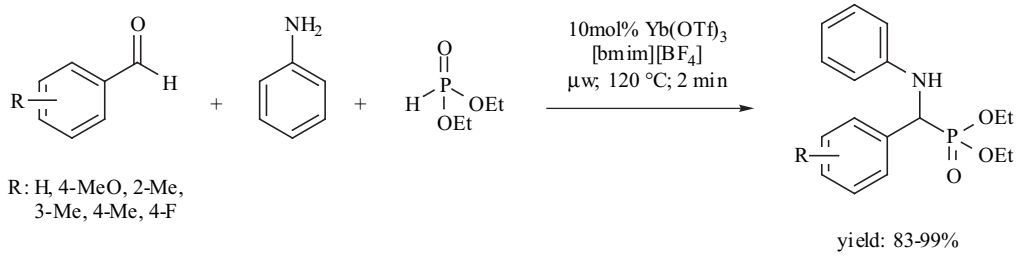
The Kabachnik-Fields reaction leading to α-amino phosphonates has gained in interest over the recent years. Lee *et al.* succeeded in demonstrating that this reaction can be improved by using microwave irradiation and ionic liquids [28]. They were able to show that $Yb(OTf)_3$ catalyses the reaction particularly effective (Scheme **18**).

Ring-closure metathesis (RCM) has been shown to be a powerful tool for the construction of ring systems. Kiddle has been studying ways to accelerate RCM using microwave irradiation [29]. In their hands, the second generation Grubbs catalyst proved to be the reagent of choice being superior compared with the Schrock-catalyst or the original Grubbs catalyst. The group was able to show, that in most cases nearly quantitative conversion could be obtained in extremely short reaction times (Scheme **19**), thus the conditions described being a marked improvement over classical conditions.

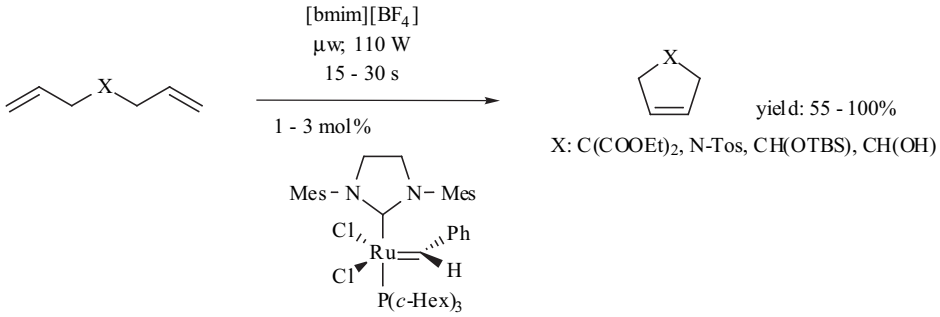
In the course of the preparation of a fragment for the total synthesis of spongistatin 1 it could be shown that the



Scheme 17. Transfer hydrogenation.



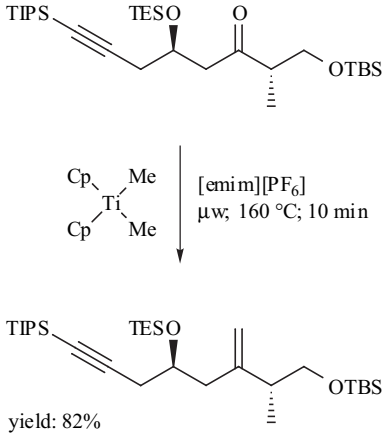
Scheme 18. Kabachnik-Fields reaction.



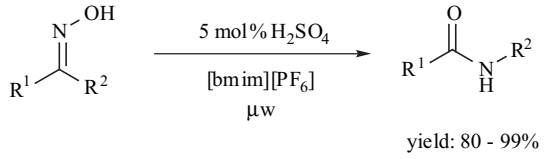
Scheme 19. Olefin metathesis.

methylenation of a ketone using the Petasis reagent was much more efficient when carried out under microwave heating [30]. The alkene was obtained in good yield after a short reaction time. Classical reaction conditions resulted in lower yield and prolonged heating. The protecting group on the acetylene moiety was essential for the success of the reaction (Scheme **20**).

In the course of studies into the properties of ionic liquids the microwave-assisted Beckmann rearrangement of ketoximes in the presence of a small amount of mineral acid was found to be particularly efficient [14]. The work showed that the rearrangement of acyclic oximes occurred within 60 seconds of irradiation, while the rearrangement of a cyclic oxime proceeded much slower (Scheme **21**).



Scheme 20. Methylenation of a ketone.



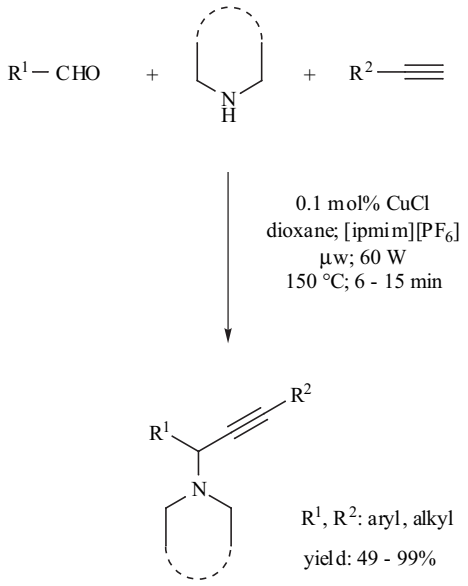
R^1: Et, Ph

R^2: 4-ClPh, 4-Tol, 4-MeOPh, Ph, Et

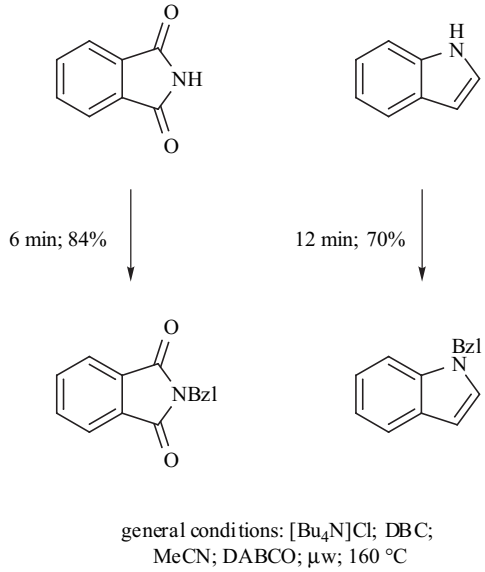
Scheme 21. Beckmann rearrangement.

Leadbeater demonstrated that Mannich-type three component condensation reactions were possible using a focussed microwave system to irradiate ionic liquid-doped reaction solutions [31]. They were able to show that the protocol they have been developing for solution phase chemistry is also amenable for solid phase organic chemistry, although the yields in the latter case are only moderate (Scheme **22**). The alkyne could also be replaced by sodium cyanide, but again the yield obtained was variable.

Shieh has noted that the DABCO-catalysed *N*-benzylation using dibenzyl carbonate proceeds well in ionic liquids [32a]. Upon subjecting the reaction mixture to microwave irradiation, a further rate enhancement was observed (Scheme **23**). The reaction times thus could be shortened from days to just minutes, while at the same time in some cases even improving the isolated yield. Although all ionic liquids gave more or less similar results when used as an additive to an organic solvent (acetonitrile), tetra-*n*-butyl ammonium chloride outperformed the imidazolium ionic liquid; a circumstance already noted earlier in a different context [32b].



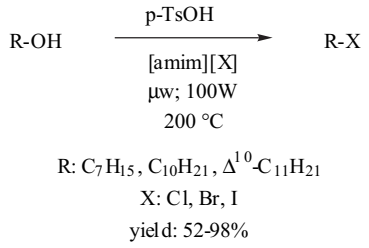
Scheme 22. Mannich-type 3 component condensation.



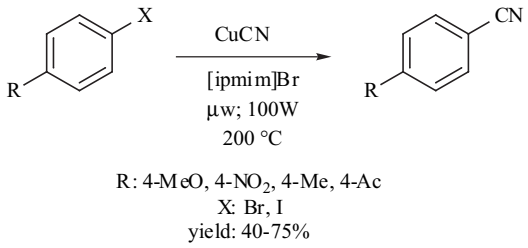
Scheme 23. *N*-benzylation with dibenzyl carbonate.

Research by Leadbeater recently showed the rapid preparation of primary alkyl halides from the corresponding alcohols [33]. The method is based on the thermal instability of ionic liquids with halide counter ions at elevated temperatures. In the presence of an acid (like *p*-toluene sulfonic acid) alcohols undergo transformation into halides (Scheme **24**). The authors were able to show, that in some cases the use of a co-solvent was beneficial for the reaction since the alkyl halide formed is extracted into the organic solvent and thus protected from decomposition. Noteworthy was the drastic reduction in reaction time applying microwave irradiation (three minutes instead of 24 - 48 hours).

In the same report the authors presented the microwave-assisted preparation of aryl nitriles starting from the corresponding aryl iodides and an excess of copper cyanide (Rosenmund-von Braun-reaction). The nitriles were obtained in moderate to good yields (Scheme **25**).



Scheme 24. Transformation of alcohols to halides.



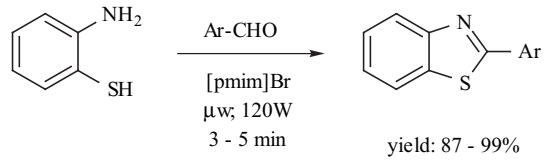
Scheme 25. Microwave-assisted Rosenmund-von Braun reaction.

After the initial research by Bazureau [19] the microwave-assisted Knoevenagel reaction recently was rediscovered by Shao and by Li [34, 35]. Both their reports describe, independently, the reaction of aromatic aldehydes with malonates. While Shao carried out the reaction in neat [bmim]BF_4 using glycine as a catalyst, Li studied the reaction in organic solvents doped with different ionic liquids. In addition, the glycine catalysed synthesis of coumarin-3-carboxylic acid ethyl ester has been achieved (Scheme **26**).

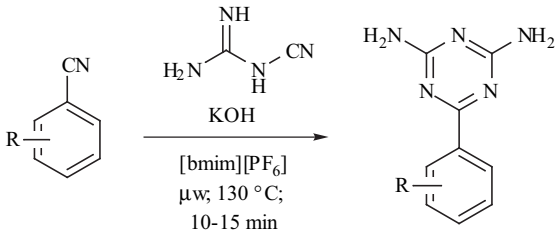
A wide variety of aromatic aldehydes undergo condensation with 2-aminothiophenol when subjected to microwave irradiation in ionic liquids [36]. The products were isolated by extraction, but no comment is made on the oxidation reaction which is also occurring during the reaction (Scheme **27**).

An efficient approach to 6-aryl-2,4-diamino-1,3,5-triazines has been presented by Song [37]. The cyclisation of dicyandiamide with various aromatic nitriles was achieved with short reaction times and good yields (Scheme **28**).

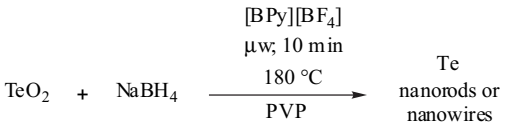
By way of contrast to the typical application of ionic liquids in organic chemistry, their use in inorganic processes is still in its infancy. In the first report Zhu detailed the preparation of tellurium single-crystalline nanorods and nanowires by microwave-assisted reduction of TeO_2 in an ionic liquid [38]. The group was able to show that these highly ordered nanostructures were formed only under controlled experimental conditions (Scheme **29**). The authors suggested the presence of anisotropic micro-domains induced by the microwave-field in the reaction system causing the anisotropic crystal growth. Nanorods and nanowires exhibit interesting properties which generally differ significantly from the bulk properties of the material.



Scheme 27. Synthesis of arylbenzothiazoles.



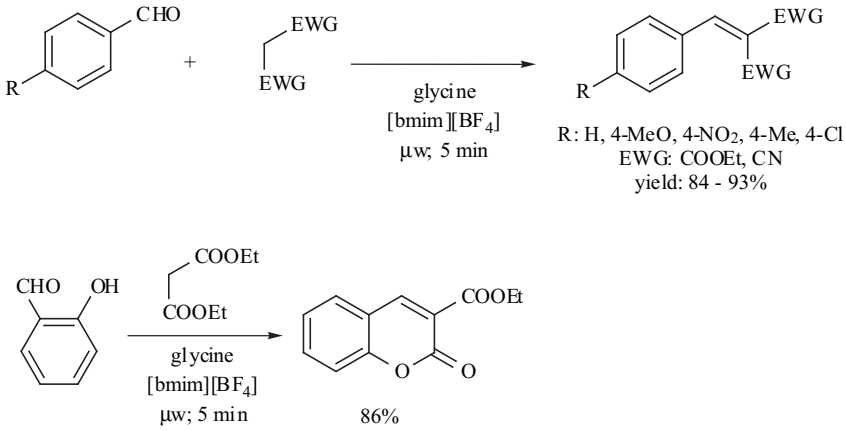
Scheme 28. Synthesis of 6-aryl-2,4-diamino-1,3,5-triazines.



Scheme 29. Synthesis of single crystal Te nanorods.

APPLICATION OF IONIC LIQUIDS UNDER ULTRASONICATION CONDITIONS

The stability of ionic liquids under sonication conditions has recently been investigated [39]. Using GC-MS spectrometry and carrying out multibubble



Scheme 26. Knoevenagel reaction.

sonoluminescence spectroscopy the authors were able to show that ionic liquids do undergo decomposition in the low (0.5) ppt range under the conditions studied. This instability is due to the extreme temperatures reached in a collapsing bubble. Since the reaction times for processes being carried out in ionic liquids are generally short, this decomposition should not be overestimated.

Ultrasound-promoted reactions in ionic liquids at ambient conditions have been extensively investigated by Srinivasan *et al.* Following a special interest in palladium-catalysed reactions the group investigated in particular the application of Pd-carbene complexes. They first studied the formation of such complexes which were formed from a Pd(II)-source (like $PdCl_2$ or $Pd(OAc)_2$) and the ionic liquid used in the study ([bbim]Br or [bbim][BF_4]). The authors regarded it highly probable that the complex ***2*** (Figure **5**) was the immediate precursor for the active zero-valent Pd-species. The *in situ* generation of this species should occur by electron-transfer processes under sonochemical conditions, primarily through the phenomenon of cavitation by means of formation and adiabatic collapse of bubbles.

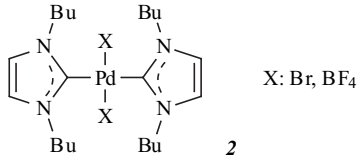
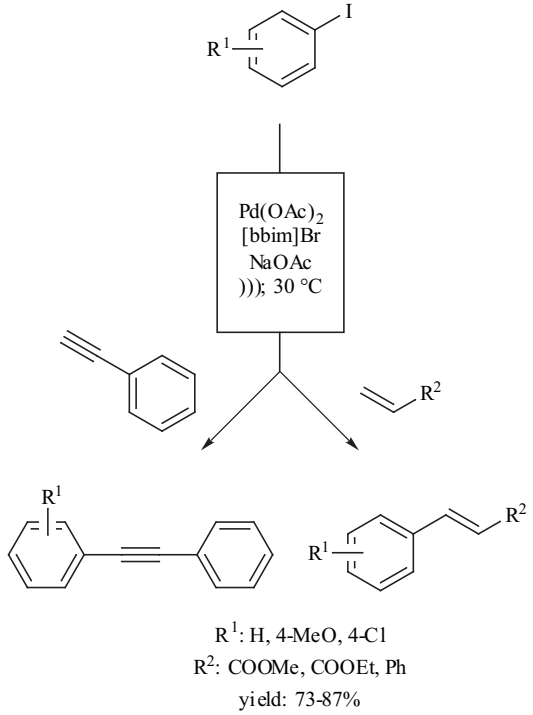


Fig. (5). Pd-carbene complex precursor.

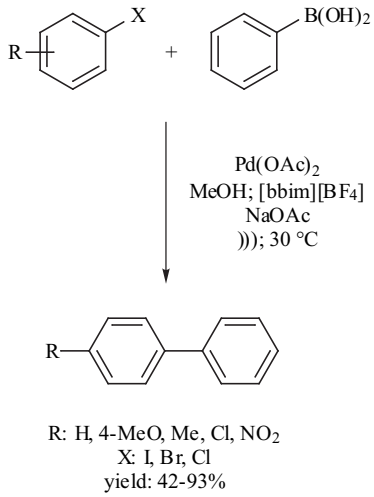
The reactivity of such a catalyst could be shown in an ultrasound-assisted Heck reaction [40]. The authors were able to demonstrate that iodobenzenes smoothly react at ambient temperature with alkenes and alkynes, resulting in good isolated yields (Scheme **30**). Transmission electron microscopy analysis of the reaction mixture evidenced the presence of nearly spherical palladium clusters.



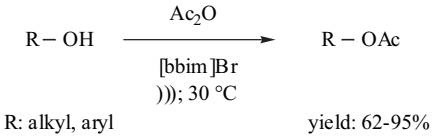
Scheme 30. Ultrasound-promoted Heck reaction.

Following these reports, Srinivasan and co-workers have been able to achieve the Pd-catalysed Suzuki cross-coupling of haloarenes with phenylboronic acid at ambient temperature [41]. The reaction progressed in the absence of a phosphine ligand in [bbim][BF_4] with methanol as a co-solvent under ultrasonic irradiation (Scheme **31**). The presence of inert gas atmosphere was found to be necessary to prevent homocoupling of the boronic acid in some cases. The authors observed the formation of a significant amount of inactive Pd black preventing the recycling of the catalyst system although they were able to overcome this problem by pre-formation of the catalyst system ***2***. In the case of less reactive chlorides, sodium methoxide was employed as base.

Srinivasan also studied the ultrasound-promoted acetylation of alcohols in ionic liquids [42]. He was able to show that a variety of alcohols undergo readily the *O*-acetylation at ambient temperature without the need to add an acylation catalyst (Scheme **32**). The role of the ultrasound in this reaction could be evidenced by the fact that corresponding reactions without ultrasound needed much longer time for complete conversion.



Scheme 31. Ultrasound-promoted Suzuki coupling.

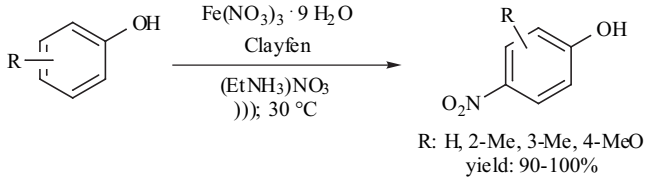


Scheme 32. Ultrasound-promoted acetylation of alcohols.

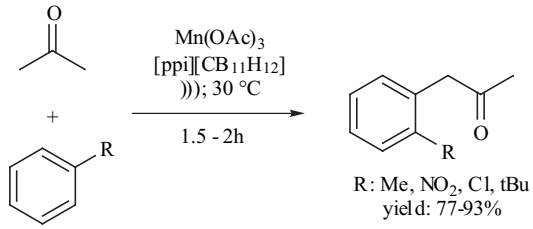
Employing ferric nitrate or ferric nitrate supported on Clayfen in ethyl ammonium nitrate phenols can be *para*-nitrated with high selectivity and short reaction times when subjected to ultrasonication [43]. The conversion to the product was essentially quantitative, the selectivity observed generally good (Scheme **33**). In the case of *para*-substituted phenols *ortho*-nitration was observed.

Yinghuai *et al.* investigated the acetonylation of arenes [44]. They were able to show that this manganese(III)-promoted radical reaction occurs in high yield and excellent selectivity when carried out in an ionic liquid under ultrasound irradiation (Scheme **34**). In the course of these studies, they introduced a new ionic liquid composed of the *N*-*n*-pentylpicolinium cation and an icosahedral anion, 1-carba-*closo*-dodecaborate. This anion is weakly coordinating,

possesses no lone pairs of electrons and is oxidatively stable. It should be noted that the results obtained in this ionic liquid with regards to yield and selectivity were superior to those obtained in other ionic liquids, like [bmim][PF_6] or [omim][BF_4]. When carried out in a classical solvent like acetic acid, the yields drop significantly.



Scheme 33. *Para*-selective nitration of phenols.



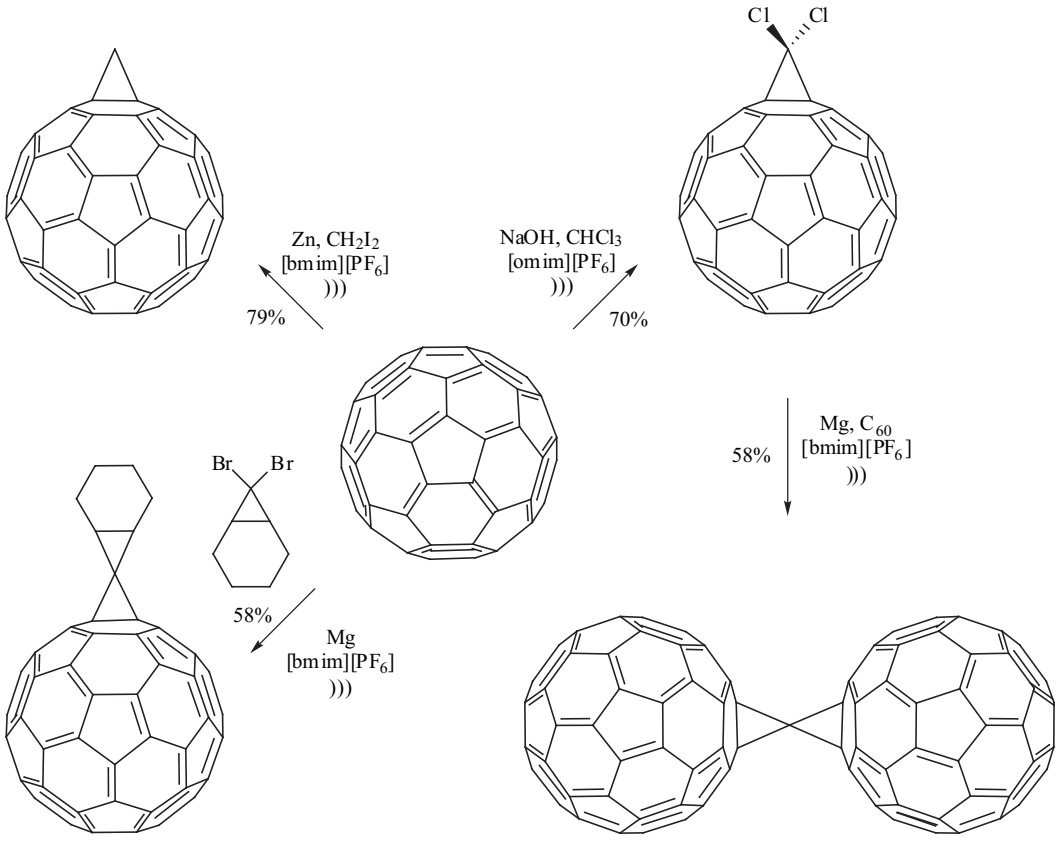
Scheme 34. Synthesis of arylacetones.

As most routes to functionalised fullerenes *via* carbenes are low yielding a route was devised using an ultrasound-promoted reaction in an ionic liquid (Scheme **35**). This new method provides the desired molecules and good yield [45]. The reaction times however remained in the range of three to four days.

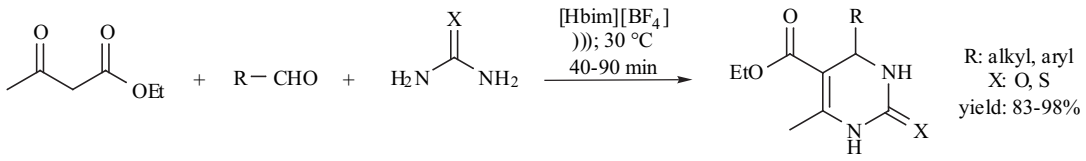
By adapting the Biginelli reaction to an ionic liquid version Srinivasan succeeded in the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones [46]. The researchers were able to show that [Hbim][BF_4] efficiently catalyses the one-pot three component condensation (Scheme **36**). According to their investigations only the synergic effect of the combined use of ultrasound and the ionic liquid led to product formation at ambient conditions.

SUMMARY

The variety of applications utilising ionic liquids in combination with microwave irradiation and ultrasonication is a testimony to the advantages those systems can bestow on many reaction processes. Their shorter reaction times, cleaner work-up procedures and unique transformations can be impressive. Their tuneable properties make them



Scheme 35. Preparation of substituted methanofullerenes.



Scheme 36. Ultrasound-promoted Biginelli 3 component condensation.

"designer solvents" which can be adapted to many different conditions.

Although there is currently considerable exploitation of the procedures and even over-emphasis in publications, we prefer to regard the methods as routine alternatives to normal procedures since there is now ample evidence for their success in effecting chemical transformations. We believe that the adoption of these methods can be very useful, especially where fast serial processing is a paramount requirement in the synthesis process.

ABBREVIATIONS

Adm = Adamantyl

All = Allyl

[amim] = 1-alkyl-3-methylimidazolium

Ar = Aryl

[bbim] = 1,3-di-*n*-butylimidazolium

[bmim] = 1-*n*-butyl-3-methylimidazolium

[BMP] = 3-methyl-*N*-butyl-pyridinium

bp = Boiling point

[BPy] = *N*-butyl-pyridinium

Bu = Butyl

Bzl = Benzyl

Cp = Cyclopentadienyl

DBC = Dibenzyl carbonate

DCE = 1,2-dichloroethane

[emim] = 1-ethyl-3-methylimidazolium

Et = Ethyl

EWG = Electron withdrawing group (e.g. CN, COOMe, COOEt)

FCC = Federal Communications Commission (US government agency regulating communications and assigning frequencies)

[Hbim] = 1-*n*-butylimidazolium

Hex = Hexyl

[ipmim] = 1-*i*-propyl-3-methylimidazolium

[4MBP] = 4-methyl-*N*-butyl-pyridinium

Me = Methyl

Mes = Mesityl

[omim] = 1-*n*-octyl-3-methylimidazolium

OTf = Triflate

Ph = Phenyl

pHOTs = *p*-toluene sulfonic acid

[pmim] = 1-*n*-pentyl-3-methylimidazolium

[ppi] = *N*-*n*-pentylpicolinium

ppt = Parts per thousand

Pr = Propyl

PVP = Poly(vinylpyrrolidone)

quant = Quantitative

RCM = Ring closure metathesis

T = Temperature

TBS = *t*-butyldimethylsilyl

TES = Triethylsilyl

THF = Tetrahydrofuran

THP = Tetrahydropyranyl

TIPS = Triisopropylsilyl

Tos = Tosyl

w/o = Without

μw = Microwave

))) = Ultrasound

REFERENCES

[1] (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399; (d) Zhao, D.; Wu, M.; Ko, Y. Min, E. *Catalysis Today* **2002**, *74*, 157; (e) Handy, S.T. *Chem. Eur. J.* **2003**, *9*, 2938; (f) Wasserscheid, P.; Welton, T. (eds.) *Ionic Liquids in Synthesis*, Wiley-VCH: Weinheim, **2002**. (g) Leadbeater, N.E.; Torenius, H.M.; Tye, H. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 511.

[2] Westman, J. WO 00/72956 A1; US 6,596,130.

[3] Varma, R.S.; Namboodiri, V.V. *Pure Appl. Chem.* **2001**, *73*, 1309.

[4] Varma, R.S.; Namboodiri, V.V. *Chem. Commun.* **2001**, 643.

[5] Namboodiri, V.V.; Varma, R.S. *Chem. Commun.* **2002**, 342.

[6] Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* **2002**, *43*, 5381.

[7] Law, M.C.; Wong, K.-Y.; Chan, T.K. *Green Chem.* **2002**, *4*, 328.

[8] Khadilkar, B.M.; Rebeiro, G.L. *Org. Proc. Res. Dev.* **2002**, *6*, 826.

[9] Deetlefs, M.; Seddon, K.R. *Green Chem.* **2003**, *5*, 181.

[10] Thanh, G.V.; Pegot, B.; Loupy, A. *Eur. J. Org. Chem.* **2004**, 1112.

[11] Lévêque, J.-M.; Luche, J.-L.; Pétrier, C.; Roux, R.; Bonrath, W. *Green Chem.* **2002**, *4*, 357.

[12] Bonrath, W.; Lévêque, J.-M.; Luche, J.-L.; Pétrier, C. WO 03/048078 A2.

[13] Leadbeater, N.E.; Torenius, H.M. *J. Org. Chem.* **2002**, *67*, 3145.

[14] Lee, J.K.; Kim, D.-C.; Song, C.E.; Lee, S.-g. *Synth. Commun.* **2003**, *33*, 2301.

[15] Hoffmann, J.; Nüchter, M.; Ondruschka, B.; Wasserscheid, P. *Green Chem.* **2003**, *5*, 296.

[16] Fraga-Dubreuil, J.; Bazureau, J.P. *Tetrahedron Lett.* **2000**, *41*, 7351.

[17] Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358.

[18] (a) Baxendale, I.R; Lee, A.-L.; Ley, S.V. *Synlett* **2001**, 1482; (b) Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850.

[19] Fraga-Dubreuil, J.; Bazureau, J.P. *Tetrahedron Lett.* **2001**, *42*, 6097.

[20] Fraga-Dubreuil, J.; Bazureau, J.P. *Tetrahedron* **2003**, *59*, 6121.

[21] Hakkou, H.; Vanden Eynde, J.J.; Hamelin, J.; Bazureau, J.P. *Tetrahedron* **2004**, *60*, 3745.

[22] Vallin, K.S.A; Emilsson, P.; Larhed M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243.

[23] Datta, G.K.; Vallin, K.S.A.; Larhed, M. *Mol. Div.* **2003**, *7*, 107.

[24] Xie, X.; Lu, J.; Chen, B.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 809.

[25] Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541.

[26] Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* **2002**, *67*, 7904.

[27] Berthold, H.; Schotten, T.; Hönig, H. *Synthesis* **2002**, 1607.

[28] Lee, S.-g.; Lee, J.K.; Song, C.E.; Kim, D.-C. *Bull. Korean Chem. Soc.* **2002**, *23*, 667.

[29] Mayo, K.G.; Nearhoof, E.H.; Kiddle, J.J. *Org. Lett.* **2002**, *4*, 1567.
[30] Gaunt, M.J.; Jessiman, A.S.; Orsini, P.; Tanner, H.R.; Hook, D.F.; Ley, S.V. *Org. Lett.* **2003**, *5*, 4819.
[31] Leadbeater, N.E.; Torenius, H.M.; Tye, H. *Mol. Div.* **2003**, *7*, 135.
[32] (a) Shieh, W.-C.; Lozanov, M.; Repič, O. *Tetrahedron Lett.* **2003**, *44*, 6943; (b) Ley, S.V.; Ramarao, C.; Smith, M.D. *Chem. Commun.* **2001**, 2278.
[33] Leadbeater, N.E.; Torenius, H.M.; Tye, H. *Tetrahedron* **2003**, *59*, 2253.
[34] Shao, G.-q. *Chin. J. Synth. Chem.* **2003**, *11*, 440.
[35] Xu, X.-M.; Li, Y.-Q.; Zhou, M.-Y.; Tan, Y.-H. *Chin. J. Org. Chem.* **2004**, *24*, 184.
[36] Ranu, B.C.; Jana, R.; Dey, S.S. *Chem. Lett.* **2004**, *33*, 274.
[37] Peng, Y.; Song, G. *Tetrahedron Lett.* **2004**, *45*, 5313.
[38] Zhu, Y.-J.; Wang, W.-W.; Qi, R.-J.; Hu, X.-L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1410.
[39] Oxley, J.D.; Prozorov, T.; Suslick, K.S. *J. Am. Chem. Soc.* **2003**, *125*, 11138.
[40] Deshmukh, R.R.; Rajagopal, R.; Srinivasan, K.V. *Chem. Commun.* **2001**, 1544.
[41] Rajagopal, R.; Jarikote, D.V.; Srinivasan, K.V. *Chem. Commun.* **2002**, 616.
[42] Gholap, A.R.; Venkatesan, K.; Daniel, T.; Lahoti, R.J.; Srinivasan, K.V. *Green Chem.* **2003**, *5*, 693.
[43] Rajagopal, R.; Srinivasan, K.V. *Ultrasonics Sonochemistry* **2003**, *10*, 41.
[44] Yinghuai, Z.; Bahnmüller, S.; Hosmane, N.S.; Maguire, J.A. *Chem. Lett.* **2003**, *32*, 730.
[45] Yinghuai, Z.; Bahnmüller, S.; Chibun, C.; Carpenter, K.; Hosmane, N.S.; Maguire, J.A. *Tetrahedron Lett.* **2003**, *44*, 5473.
[46] Gholap, A.R.; Venkatesan, K.; Daniel, T.; Lahoti, R.J.; Srinivasan, K.V. *Green Chem.* **2004**, *6*, 147.

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