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Review

REVIEW

[Bmim]PF_6: An efficient tool for the synthesis of diverse bioactive heterocycles✳

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Abstract: Heterocycles are the privileged structural subunit of many marketed drug molecules. On the other hand, the last decade has seen tremendous applications of the ionic liquid [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) as an efficient, cheap, commercially available, low toxic reaction medium for various organic transformations. The present review summarizes recent reported applications of [bmim]PF_6 as an efficient reaction medium for the synthesis of diverse biologically relevant heterocycles.

Keywords: [Bmim]PF_6; heterocycles; hexafluorophosphate; imidazolium; P-ionic liquid.

CONTENTS

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✳Dedicated to Prof. Kamal Usaf Sadek, Mania University, Mania, Egypt.
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1. INTRODUCTION

Heterocycles are the skeleton of the majority of hitherto known organic compounds.[1,2] Many synthetic compounds containing heterocycles possess immense biological activities that include anti-microbial,[3] anti-malarial,[4] anti-cancer,[5] cytotoxic,[6] anti-inflammatory,[7] anti-oxidant,[8] anti-hyperglycemic and anti-dyslipidemic,[9] along with anti-neurodegenerative disorders such as Alzheimer's and Parkinson disease and many more.[10–12]

Among the other significant parameters, screening of suitable reaction medium plays the key role during organic transformations.[13,14] Worldwide, scientists are trying to modify the reaction media to increase the efficiency of the reaction and reduce their toxicity level as well. In recent times, a wide range of ionic liquids have been employed as reaction media due to their inherent features that include high thermal stability, ability to dissolve a large number of organic and inorganic compounds, non-volatility, low inflammability, easy reusability *etc.*[15–29] The organic and ionic environment in ionic liquids renders almost all kinds of interactions with reactants. This may cause a reduction in activation energies, either by stabilizing the transition states or by destabilizing the reactants.[30,31] Moreover, both ionic and van der Waals interactions with solutes generate internal pressure in an ionic liquid, which eventually accelerates the chemical reaction by promoting an accumulation of reactants in the cavities of the solvent.[32–34] Recyclability of ionic liquid makes a protocol cost effective as well.

Due to these above-mentioned advantages, ionic liquids are being used in many organic transformations as both reaction medium as well as promoter even in the absence of any other catalyst.[35–40]

Recently, among the others, ionic liquids based on imidazolium salts, have gained significant attention as efficient reaction media and have found immense applications in various organic synthesis that include hydrogenations,[41] Friedel–Crafts reactions,[42] Heck reactions,[43] Bishler–Napieralski reactions,[44] Henry reaction[45] and many more.[46] Some of the ionic liquids based on the 1-butyl-3-methylimidazolium cation are presented in Fig. 1. Among these, during few years, the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) has shown tremendous applications in various organic transformations.[47–50]

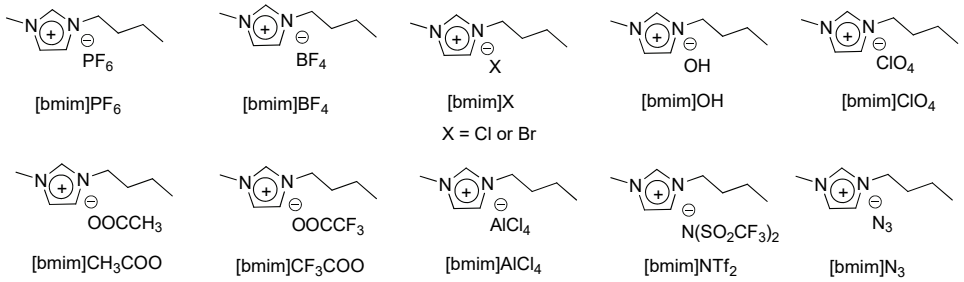


Fig. 1. Some of the 1-butyl-3-methylimidazolium based ionic liquids.

The present review deals with the applications of the ionic liquid [bmim]PF_6 for the synthesis of diverse bioactive heterocycles, and when possible, gives a comparison of its efficiency with the rest of the hitherto reported congeners.

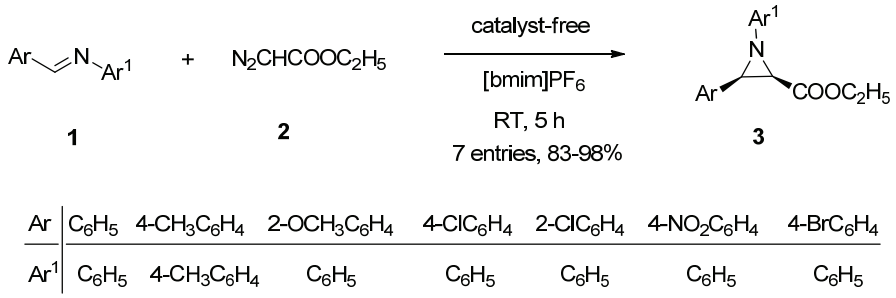
2. SYNTHESIS OF *N*-HETEROCYLCES

2.1. Synthesis of aziridines

Aziridines are used as an important precursor for the synthesis of a wide range of nitrogen-containing heterocycles.[51,52] A simple, efficient and stereo-selective method was developed for the synthesis of aziridines (**3**) in the reaction between various imines (**1**) and ethyl diazoacetate (**2**) under catalyst-free conditions in the ionic liquid [bmim]PF_6 at room temperature (Scheme 1).[53] After completion of the reaction, the ionic liquid was recovered easily and reused five times without any loss in its activity. Mild reaction conditions, good yields and high product selectivity are some of the advantages of this protocol.

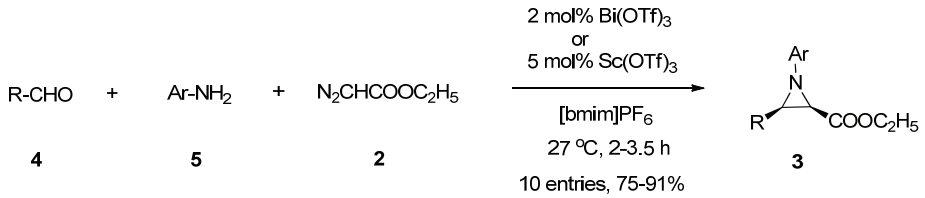
In the same year, another method was reported for the synthesis of *cis*-diastereoselective aryl aziridines (**3**) *via* three-component reactions of aldehydes (**4**), various amines (**5**) and ethyl diazoacetate (**2**) using $Bi(OTf)_3$ or $Sc(OTf)_3$ as catalyst in the same ionic liquid at 27 °C (Scheme 2).[54] The use of a catalyst red-

uces the reaction time as compared to the catalyst-free conditions (Scheme 1). Ambient reaction condition, wide range of substrate tolerance, reusability of the media, high atom economy, good to excellent yields are some of the major benefits of this developed protocol.



Ar	C_6H_5	4-$CH_3C_6H_4$	2-$OCH_3C_6H_4$	4-ClC_6H_4	2-ClC_6H_4	4-$NO_2C_6H_4$	4-BrC_6H_4
Ar^1	C_6H_5	4-$CH_3C_6H_4$	C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5

Scheme 1. [Bmim]PF_6-mediated synthesis of aziridines at room temperature.



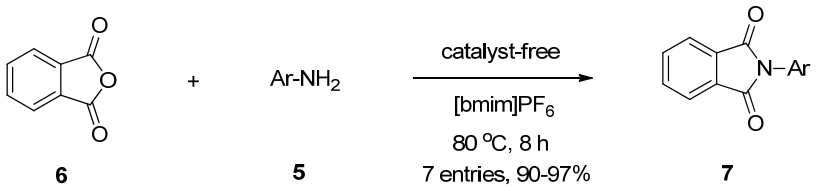
R = C_6H_5 & Ar = C_6H_5, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-OHC_6H_4, 4-$NO_2C_6H_4$

R	4-ClC_6H_4	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	$C(CH_3)_3$	C_5H_{11}
Ar	4-ClC_6H_4	4-ClC_6H_4	C_6H_5	C_6H_5	4-ClC_6H_4

Scheme 2. [Bmim]PF_6-mediated triflate salts catalyzed three-component synthesis of aziridines.

2.2. Synthesis of N-*substituted phthalimides*

The ionic liquid [bmim]PF_6 was found to be an efficient alternative to classical solvents for the synthesis of *N*-substituted phthalimides.[55–57] A series of *N*-substituted phthalimides (**7**) was synthesized in good yields *via* the reaction of succinic anhydride (**6**) and various aryl amines (**5**) under catalyst-free conditions in [bmim]PF_6 at 80 °C (Scheme 3).[55] The ionic liquid was recovered and reused many times. In the next year, along with succinic anhydride, Le *et al.*[56] also employed maleic and phthalic anhydride for the synthesis of *N*-aryl phthalimides in the ionic liquid [bmim]PF_6 at 140 °C. Under these optimized conditions, reactions with aliphatic amines also proceeded smoothly to produce the desired products in high yields.

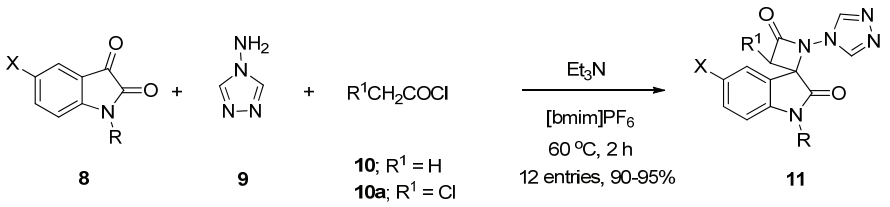


Ar = C_6H_5, 2-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-Br-C_6H_4, 1-naphthyl

Scheme 3. [Bmim]PF_6-mediated synthesis of *N*-substituted phthalimides.

2.3. Synthesis of spiro*[azetidine-2,3′-(3*H*)indole] derivatives*

Azetidinones are very common in many biologically active compounds having significant biological efficacies that include anti-bacterial, anti-fungal,[58] and anti--inflammatory[59] activities. A series of novel spiro[azetidine-2,3′-(3*H*)indole] derivatives (**11**) was synthesized by the reactions of isatins (**8**), 4-amino-4*H*-1,2,4-triazole (**9**) and acetyl chloride (**10**) or chloroacetyl chloride (**10a**) in ionic liquid [bmim]PF_6 using triethylamine as catalyst at 60–70 °C (Scheme 4).[60] The ionic liquid was recovered easily and reused twice without any loss in its activity. The insecticidal activities of the synthesized compounds were tested against *Periplaneta americana* and few were found to possess prominent efficacy.



when R^1 = H					
R	H	CH_3	$CH_2C_6H_5$	$CH_2N(CH_3)_2$	$CH_2N(C_2H_5)_2$
X	Cl	F	H	H	H

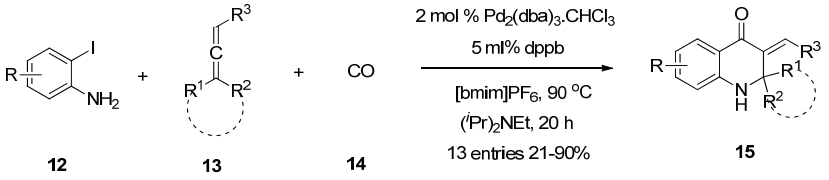
when R^1 = Cl							
R	$CH_2N(CH_2)_5$	$COCH_3$	H	H	H	CH_3	$CH_2N(CH_3)_2$
X	H	H	H	Cl	F	H	H

Scheme 4. [Bmim]PF_6-mediated synthesis of spiro[azetidine-2,3′-(3*H*)indole derivatives.

*2.4. Synthesis of 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones*

The ionic liquid [bmim]PF_6 was found to be an efficient medium for the palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines (**12**), various allenes (**13**) and carbon monoxide (**14**) to afford the corresponding 3-methylene--2,3-dihydro-1*H*-quinolin-4-ones (**15**) in the presence of a catalytic amount of

1,4-bis(diphenylphosphino)butane (dppb) and diisopropylethylamine [(^{i}Pr)$_2$NEt] as promoter at 90 °C (Scheme 5).[61] The entire medium containing the catalyst as well as the promoter was successfully recovered and reused more than four times without significant loss in activities.



R^3 = H; R^1 & R^2 = CH_3; R = H, 4-CH_3, 4-Cl, 5-OCH_3, 4,5-diCH_3

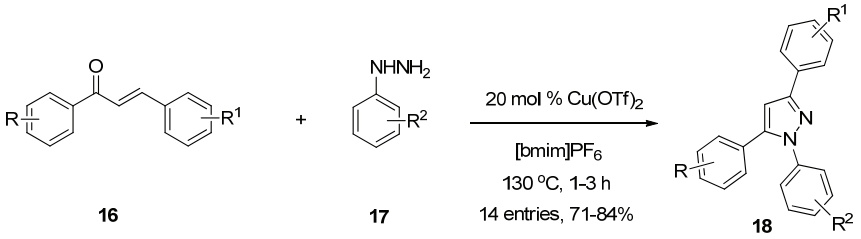
R^3 = H; R^1 & R^2 = -$(CH_2)_5$-; R = H, 4-CH_3, 5-OCH_3, 4,5-diCH_3

R^1	H	H	H	H
R^2	C_3H_7	CH_3	C_6H_5	COOEt
R^3	C_3H_7	$CH_2C_6H_5$	CH_3	CH_3
R	H	H	H	H

Scheme 5. [Bmim]PF_6-mediated synthesis of 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones.

2.5. Synthesis of 1,3,5-triarylpyrazoles

Heterocycles containing the pyrazole moiety have exhibited diverse biological activities that include anti-depressant, anti-convulsant,[62] anti-inflammatory and anti-arthritic[63] activities. A simple, efficient, and environmentally benign protocol was developed for the synthesis of 1,3,5-triarylpyrazoles (**18**) *via* the one-pot oxidative addition of chalcones (**16**) and arylhydrazines (**17**) using $Cu(OTf)_2$ as catalyst in [bmim]PF_6 at 130 °C (Scheme 6).[64] During optimization,



R & R^1 = H; R^2 = 4-$C(CH_3)_3$, 2-CH_3, 3,4-diCl, 3-Cl-4-CH_3, 4-OCH_3

R & R^1 = 4-CH_3; R^2 = 4-$C(CH_3)_3$, 3,4-diCl, 3-Cl-4-CH_3

R = 4-OCH_3 & R^1 = H; R^2 = 3,4-diCl, 3-Cl-4-CH_3

R = 2-F & R^1 = 4-Cl; R^2 = 4-$C(CH_3)_3$, 2-CH_3

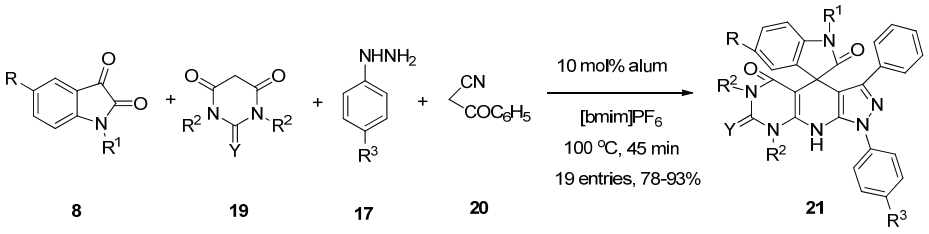
R = 4-NO_2 & R^1 = 4-OCH_3; R^2 = 4-$C(CH_3)_3$, 3-Cl-4-CH_3

Scheme 6. [Bmim]PF_6-mediated synthesis of 1,3,5-triarylpyrazoles.

it was found that other metal triflates such as $Sc(OTf)_3$, $Ce(OTf)_3$, AgOTf, $Zn(OTf)_2$ and $Yb(OTf)_3$ as catalyst in $[bmim]PF_6$ produced lower yields. On the other hand, $Cu(OTf)_2$ yielded lower product in $[bmim]BF_4$ and [bmim]Br compared to in $[bmim]PF_6$. The catalyst along with the reaction media was successfully recovered and reused four times without loss in catalytic activity. The synthesized compounds were found to possess antiproliferative efficacies.

*2.6. Synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]triones*

A simple, efficient and practical protocol was developed for the synthesis of a series of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]trione derivatives (**21**) *via* one-pot four-component reactions between isatins (**8**), barbituric acids (**19**), phenylhydrazines (**17**) and 3-oxo-3-phenylpropanenitrile (**20**) using alum $KAl(SO_4)_2{\cdot}12H_2O$ as a reusable catalyst in $[bmim]PF_6$ at 100 °C (Scheme 7).[65]



Y = O; R^1, R^2, R^3 = H; R = H, Br, NO_2, CH_3

Y = O; R^2, R^3 = H; R^1 = CH_3; R = H, Br, NO_2

Y = O; R^2, R^3 = H; R^1 = C_2H_5; R = H, Br

Y = S; R^2, R^3 = H, R^1= CH_3; R = Br, NO_2

Y = S; R^2, R^3, R = H, R^1= CH_3

Y = O; R^2 = CH_3; R^3 = H

R^1	H	H	CH_3
R	Br	NO_2	H

Y = O; R^2 = H, R^3 = NO_2

R^1	H	H	H	CH_3
R	H	Br	NO_2	H

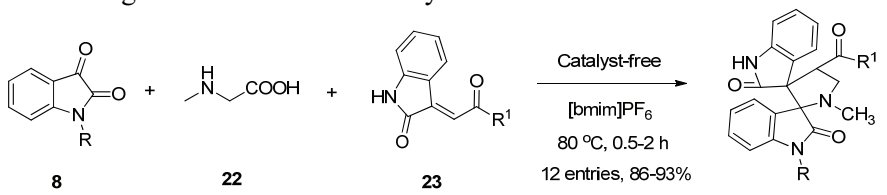
Scheme 7. $[Bmim]PF_6$-mediated synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido-[2,3-*d*]pyrimidine]triones.

During optimization, other 1-butyl-3-methylimidazolium based ionic liquids such as $[bmim]BF_4$, $[bmim]CF_3CO_2$, [bmim]Br, [bmim]Cl were also screened using alum as catalyst and among them, $[bmim]PF_6$ came out to be superior in terms of both reaction time as well as product yields. Mild reaction conditions, short reaction time, excellent yields, varieties of substrates, high atom economy and reusability of medium are some of the major advantages in this protocol. In the same year, under the same reaction conditions Shirvan *et al.*[66] also synthesized a variety of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]tri-

ones staring from substituted isatins, barbituric acids, and 1,3-diphenyl-1*H*-pyrazol-5-amines.

2.7. Synthesis of dispiropyrrolidine-bisoxindole derivatives

Spiro-oxindoles are very common in pharmacologically important compounds.[67] A simple, facile and efficient catalyst-free one-pot three-component protocol was reported for the synthesis of a series of novel dispiropyrrolidine-bisoxindole derivatives (**24**) *via* the cycloaddition between isatins (**8**), sarcosine (**22**) and 3-(aroylmethylene)-1,3-dihydro-2*H*-indol-2-one (**23**) in [bmim]PF_6 at 80 °C (Scheme 8).[68] Ionic liquid was recovered successfully and reused three times without significant loss in its activity.



8 **22** **23** **24**

R = H; R^1 = C_6H_5, 3-$OCH_3C_6H_4$, 4-F-C_6H_4

R = CH_3; R^1 = C_6H_5, 3-$OCH_3C_6H_4$, 4-F-C_6H_4

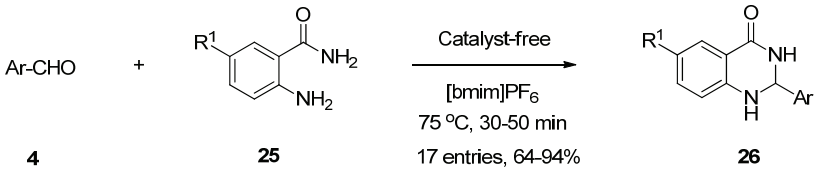
R = $CH_2C_6H_5$; R^1 = C_6H_5, 3-$OCH_3C_6H_4$, 4-F-C_6H_4

R^1 = C_4H_3S; R = H, CH_3, $CH_2C_6H_5$

Scheme 8. [Bmim]PF_6-mediated catalyst-free synthesis of dispiropyrrolidine-bisoxindoles.

*2.8. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones*

Now-a-days, performing reactions in absence of any added catalysts is one of the thrusting areas.[69–71] A series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**26**) was synthesized in moderate to high yields *via* the condensation between anthranilamides (**25**) and various aldehydes (**4**) in [bmim]PF_6 under catalyst-free conditions at 75 °C (Scheme 9).[72] Mild reaction conditions, short



4 **25** **26**

R^1 = H;
Ar = C_6H_5, 4-$OCH_3C_6H_4$, 2,4-$(OCH_3)_2$-C_6H_3, 4-$N(CH_3)_2C_6H_4$, 4-OHC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-furyl, 2-pyridyl

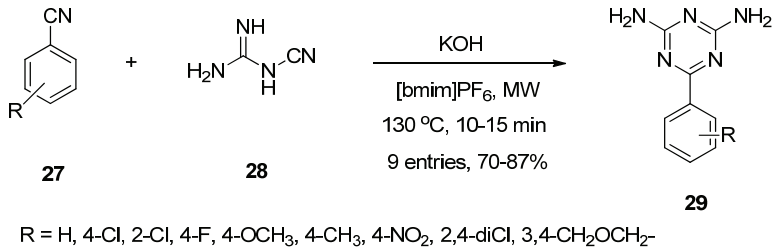
R^1 = Cl; Ar = C_6H_5, 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$

Scheme 9. [Bmim]PF_6-mediated catalyst-free synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

reaction times, good to excellent yields make this protocol attractive. A wide range of aldehydes that include electron donating as well as electron withdrawing substituent are well tolerated under the optimized reaction conditions affording the required products in good yields. During optimization, a number of other ionic liquids were also tested, whereby [bmim]PF_6 was found to be superior for this transformation. After completion of the reaction, the ionic liquid [bmim]PF_6 was successfully recovered and reused for the several runs without loss of its activity.

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

A simple, rapid and efficient microwave-assisted environmentally benign protocol was developed for the synthesis of 2,4-diamino-6-aryl-1,3,5-triazines (**29**) *via* the reaction of aromatic nitriles (**27**) and dicyanodiamide (**28**) using KOH as catalyst in [bmim]PF_6 at 130 °C (Scheme 10).[73] In the absence of microwave, *i.e.*, under conventional heating at the same temperature, the reaction took more than 8 h to complete and yields of the corresponding products were also lower. [Bmim]PF_6 was found to be superior to [bmim]BF_4 for this conversion. After completion of the reaction, the ionic liquid was successfully recovered and recycled five times without significant loss in its activity.



R = H, 4-Cl, 2-Cl, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2, 2,4-diCl, 3,4-CH_2OCH_2-

Scheme 10. [Bmim]PF_6-mediated synthesis of 2,4-diamino-6-aryl-1,3,5-triazines under microwave conditions.

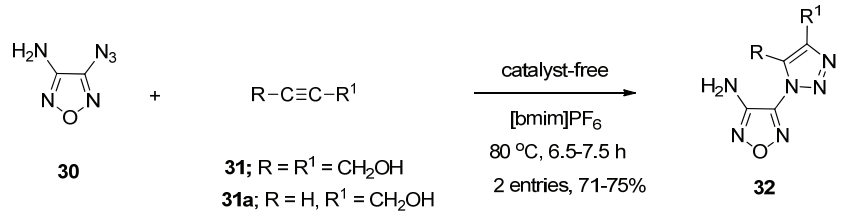
*2.10. Synthesis of 4-(1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazol-3-amine derivatives*

Seregin *et al.*[74] synthesized 4-(1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazol-3-amines (**32**) *via* the 1,3-dipolar cycloaddition between 4-amino-3-azidofurazan (**30**) and butynediol (**31**) or propargyl alcohol (**31a**) in [bmim]PF_6 under catalyst-free conditions at 80 °C (Scheme 11). The use of the ionic liquid [bmim]BF_4 produced lower yields.

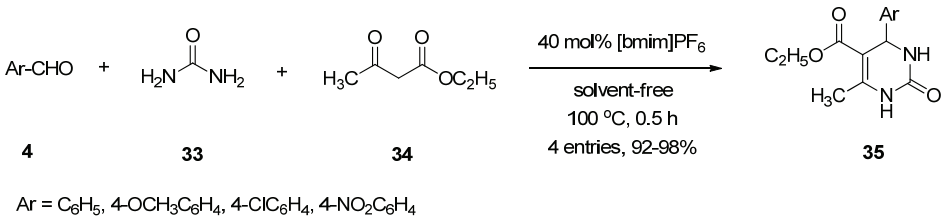
*2.11. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones*

Dihydropyrimidinones possess significant biological efficacies that include anti-viral, anti-bacterial, anti-hypertensive and anti-tumour activity.[75] A series of 3,4-dihydropyrimidin-2(1*H*)-ones (**35**) were synthesized in good yields *via* the one-pot, three-component Biginelli reaction[76] of various aromatic aldehydes (**4**),

urea (**33**) and ethyl acetoacetate (**34**) using a catalytic amount of ionic liquid [bmim]PF_6 under solvent-free conditions at 100 °C (Scheme 12).[77] For this transformation, the ionic liquid [bmim]BF_4 was found to be as efficient as [bmim]PF_6, whereas [bmim]Cl afforded lower yields.



Scheme 11. [Bmim]PF_6-mediated synthesis of 4-(1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazol-3--amines.



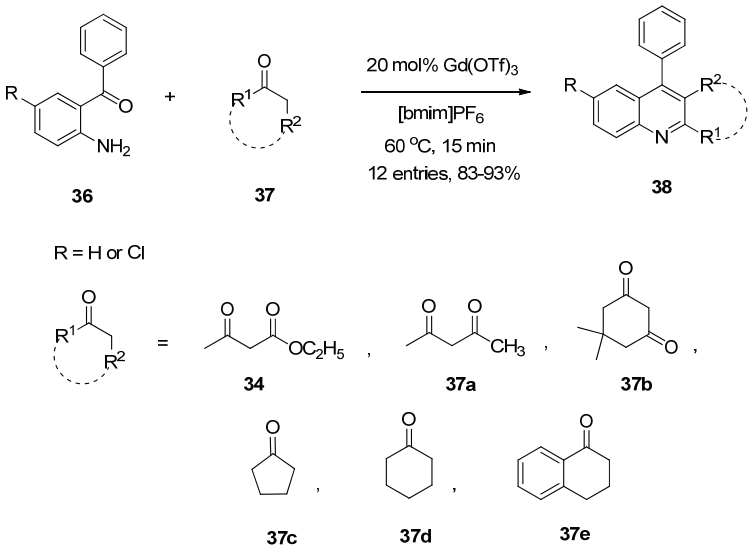
Scheme 12. [Bmim]PF_6-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

2.12. Synthesis of quinolines

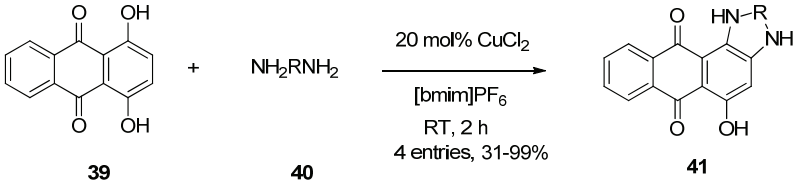
A mild, simple and efficient protocol was developed for the synthesis of a variety of quinoline derivatives (**38**) by following the Friedländer annulation reaction[78] of *o*-aminobenzophenone (**36**) and various ketones (**34**, **37a-e**) using gadolinium triflate [Gd(OTf)$_3$] as an inexpensive, moisture-stable Lewis acid catalyst in [bmim]PF_6 at 60 °C (Scheme 13).[79] After completion of the reaction, the catalyst containing ionic liquid was successfully recovered and reused several times without appreciable loss in product formation. Mild reaction conditions, operational simplicity, very short reaction time; high yields of products are some of the major advantages of this developed protocol.

2.13. Synthesis of anthraquinone fused N-heterocycles

A number of anthraquinone fused *N*-heterocycles (**41**) were synthesized *via* the ring-closure metathesis reactions of 1,4-dihydroxyanthraquinone (**39**) and various diamines (**40**) in the presence of a catalytic amount of $CuCl_2$ in the ionic liquid [bmim]PF_6 at room temperature (Scheme 14).[80] The reaction was also performed in conventional solvents, such as dimethylformamide and dichloromethane, but lower yields were obtained. The ionic liquid containing catalyst was successfully recovered and reused five times without significant loss in its activity.



Scheme 13. [Bmim]PF_6-mediated synthesis of a variety of quinoline derivatives.

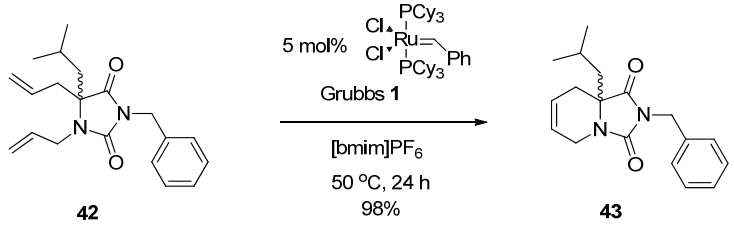


R = $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, cyclohexane-1,2-diyl, $-CH_2CH(CH_2CH_3)-$

Scheme 14. [Bmim]PF_6-mediated synthesis of anthraquinone fused *N*-heterocycles.

2.14. Synthesis of novel N-*heterocycles* via *ring-closing metathesis reactions*

The ionic liquid [bmim]PF_6 was found to be an effective medium for ring--closing metathesis using Grubbs catalysts.[81,82] A simple and straightforward protocol was demonstrated for the ring-closing metathesis of 1,5-diallyl-3-benzyl-5-isobutylimidazolidine-2,4-dione (**42**) to afford the corresponding novel 2-benzyl-8a-isobutyl-8,8a-dihydroimidazo[1,5-*a*]pyridine-1,3(2*H*,5*H*)-dione (**43**) using ruthenium based Grubbs catalyst in [bmim]PF_6 at 50 ºC (Scheme 15).[83]



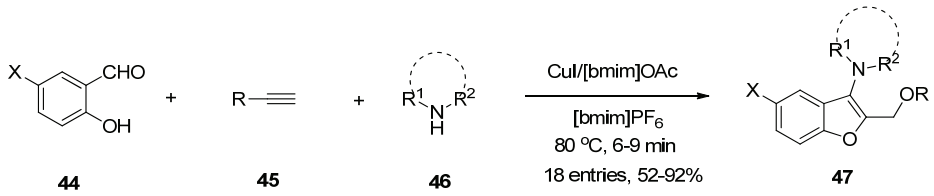
Scheme 15. [Bmim]PF_6-mediated ring-closing metathesis reaction using a ruthenium catalyst.

After completion of reaction, the ionic liquid containing the ruthenium catalyst was successfully recovered and thrice reused for the same reaction.

3. SYNTHESIS OF *O*-HETEROCYCLES

*3.1. Synthesis of 2,3-disubstituted benzo[*b*]furans*

Benzo[*b*]furan-containing heterocycles possess immense pharmaceutical efficacies that include anti-fungal[84] and anti-tumor[85] activity. A combination of CuI and 1-butyl-3-methylimidazolium acetate ([bmim]OAc) in [bmim]PF_6 was shown to be an efficient catalytic system for the synthesis of a series of 2,3--disubstituted benzo[*b*]furan derivatives (**47**) *via* one-pot three-component tandem reactions of salicylaldehyde (**44**), alkynes (**45**) and various aliphatic secondary amines (**46**), such as morpholine, dibenzylamine, piperidine *etc*., at 80 °C (Scheme 16).[86]



44 **45** **46** **47**

R = C_6H_5 or 4-$CH_3C_6H_4$; R^1 & R^2 = morpholine; X = H, Br, Cl

R = C_6H_5 or 4-$CH_3C_6H_4$; R^1 & R^2 = piperidine; X = H, Br, Cl

R = C_6H_5 or 4-$CH_3C_6H_4$; R^1 & R^2 = dibenzylamine; X = H, Br, Cl

R = -$(CH_2)_7CH_3$; R^1 & R^2 = morpholine; X = Cl

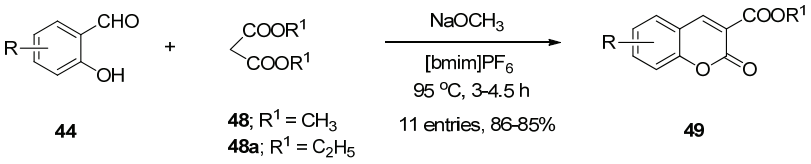
Scheme 16. [Bmim]PF_6-mediated synthesis of 2,3-disubstituted benzo[*b*]furans.

Reactions with aromatic secondary amines, such as *N*-benzylaniline or *N*-methylaniline, and aromatic primary amines, such as aniline, instead of aliphatic secondary amines did not afford the corresponding benzo[*b*]furan derivatives. In this reaction, it was also observed that aryl alkynes are more effective and produced higher yields than aliphatic alkynes. After completion of the reaction, the ionic liquid containing CuI and [bmim]OAc was recovered and recycled five times without any significant loss in its catalytic activity.

3.2. Synthesis of coumarin derivatives

Coumarins are very common in naturally occurring heterocycles possessing a wide range of pharmaceutical activities that include anti-bacterial, anti-HIV, anti-viral, anti-coagulant, anti-oxidant and anti-cancer activities.[87–90] A variety of 3-substituted coumarins (**49**) were synthesized *via* the Knoevenagel condensation of salicylaldehyde (**44**) and dialkyl malonate (**48** or **48a**) using sodium methoxide as catalyst in the ionic liquid [bmim]PF_6 at 95 °C (Scheme 17).[91]

Several other butylmethylimidazolium-based ionic liquids, such as [bmim]Cl, [bmim]BF_4, [bmim]Br and [bmim]$AlCl_4$, were also screened for the same transformation. Among them [bmim]PF_6 was found to be superior in terms of both reaction time and product yield.



44 **48**; $R^1 = CH_3$ **48a**; $R^1 = C_2H_5$ **49**

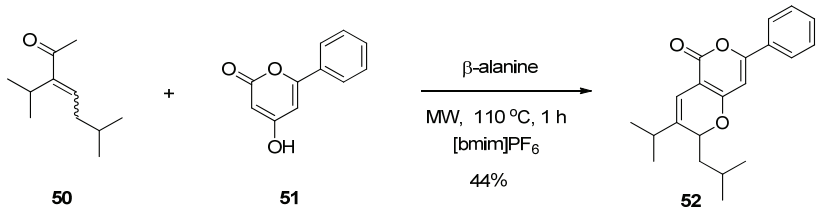
$R^1 = CH_3$; R = 4-OH, 4-OCH_3

$R^1 = C_2H_5$; R = H, 4-OH, 3-OH, 4-OCH_3, 3,4-diOH, 4-$N(C_2H_5)_2$, 3-OCH_3, 3-Br-4-OH, 3-Br-4-OCH_3

Scheme 17. [Bmim]PF_6-mediated synthesis of 3-substituted coumarin derivatives.

*3.3. Synthesis of pyrano[4,3-*b*]pyran-5-one derivative*

2-Isobutyl-3-isopropyl-7-phenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (**52**) was synthesized *via* the domino reaction between 3-isopropyl-6-methylhept-3-en-2-one (**50**) and 4-hydroxy-6-phenyl-2*H*-pyran-2-one (**51**) in the presence of a catalytic amount of *β*-alanine as catalyst in [bmim]PF_6 under microwave irradiation at 110 °C (Scheme 18).[92]

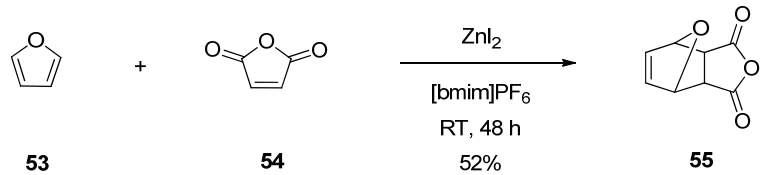


50 **51** **52**

Scheme 18. [Bmim]PF_6-mediated synthesis of a pyrano[4,3-*b*]pyran-5-one derivative.

3.4. Synthesis of epoxyisobenzofuran-1,3-dione

A simple and efficient method was developed for the synthesis of epoxyisobenzofuran-1,3-dione **55** *via* the Diels–Alder reaction of furan (**53**) and furan-2,5-dione (**54**) using ZnI_2 as promoter in [bmim]PF_6 at room temperature (Scheme 19).[93]

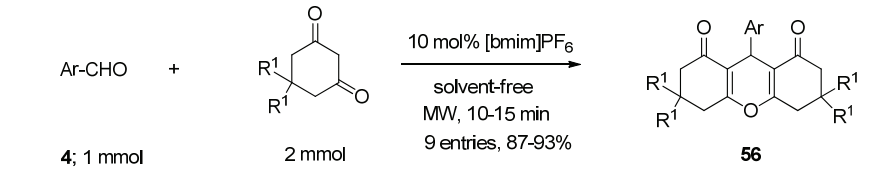


53 **54** **55**

Scheme 19. [Bmim]PF_6-mediated synthesis of an epoxyisobenzofuran-1,3-dione.

3.5. Synthesis of xanthenes

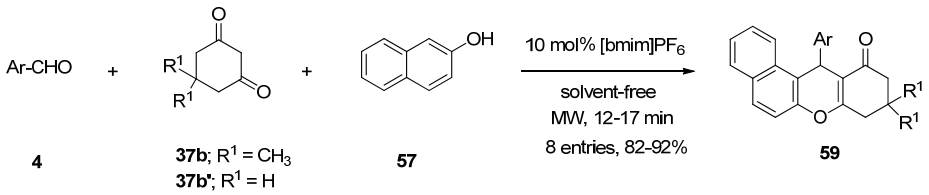
Xanthenes, in particular, 1,8-dioxo-octahydroxanthene moieties, have gained significant attention due to their potent pharmacological efficacies, such as anti--microbial, anti-cancer and enzyme inhibitory activity.[94–96] A simple, rapid and efficient protocol was reported for the synthesis of 1,8-dioxo-octahydroxanthenes (**56**) *via* one-pot pseudo three-component reactions of aromatic aldehydes (**4**) and dimedone (**37b**) or 1,3-cyclohexanedione (**37b′**) in the presence of a catalytic amount of [bmim]PF_6 under microwave irradiation and solvent-free conditions (Scheme 20).[97] Using the same optimized reaction conditions, a series of benzo-xanthenes (**59**, Scheme 21) and chromene derivatives (**60**, Scheme 22) were also synthesized starting from various aromatic aldehydes (**4**), 1,3-cyclohexanediones (**37b** or **37b′**) and *β*-naphthol (**57**) or 4-hydroxycoumarin (**58**), respectively. Very short reaction times, solvent-free conditions, high atom economy, reusability of the media and good to excellent yields are some of the major advantages of this protocol. A range of aldehydes that include electron donating and withdrawing



R^1 = H
Ar = 3,4,5-$(OCH_3)_3C_6H_2$, 3,4-$(OCH_3)_2C_6H_3$, 3,5-$(OCH_3)_2$-4-OHC_6H_2, 4-$OC_2H_5C_6H_4$, 4-$C_6H_5C_6H_4$

R^1 = CH_3
Ar = 3,4,5-$(OCH_3)_3C_6H_2$, 3,4-$(OCH_3)_2C_6H_3$, 4-$C_6H_5C_6H_4$, 3-OHC_6H_4

Scheme 20. [Bmim]PF_6-catalyzed synthesis of 1,8-dioxo-octahydroxanthenes under solvent-free conditions.

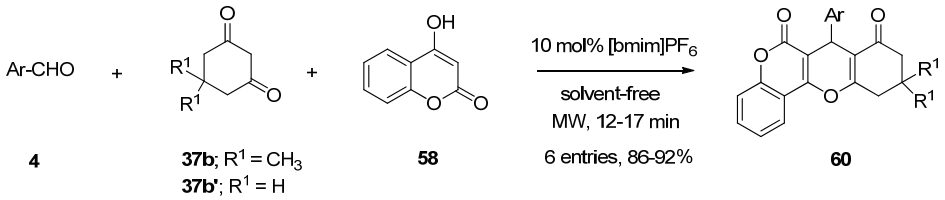


R^1 = CH_3; Ar = 3,5-$(OCH_3)_2$-4-OHC_6H_2, C_6H_5

R^1 = H
Ar = 3,4,5-$(OCH_3)_3C_6H_2$, 4-ClC_6H_4, 3,4-$(OCH_3)_2C_6H_3$, 3,5-$(OCH_3)_2$-4-OHC_6H_2, 4-$C_6H_5C_6H_4$, 3-$NO_2C_6H_4$, 2-FC_6H_4, 3-OHC_6H_4, 2-$OC_2H_5C_6H_4$

Scheme 21. [Bmim]PF_6-catalyzed synthesis of benzoxanthenes under solvent-free conditions.

substituent are well tolerated under the optimized reaction conditions and excellent yields were attained. All the synthesized compounds were screened for their anti-oxidant properties and some of them were found to possess significant anti-oxidant efficacies.

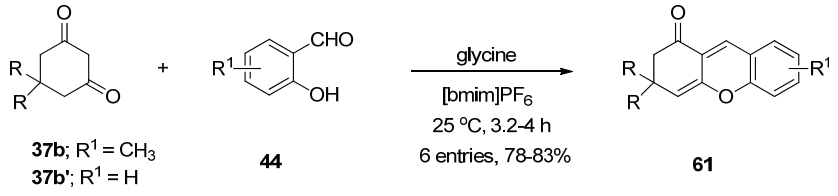


$R^1 = CH_3$; Ar = 3,5-$(OCH_3)_2$-4-OHC_6H_2

R^1 = H
Ar = 3,4,5-$(OCH_3)_3C_6H_2$, 3,4-$(OCH_3)_2C_6H_3$, 3,5-$(OCH_3)_2$-4-OHC_6H_2, 4-$C_6H_5C_6H_4$, 3-FC_6H_4, 4-OHC_6H_4, 3-OHC_6H_4

Scheme 22. [Bmim]PF_6-catalyzed synthesis of chromenes under solvent-free conditions.

Another efficient protocol was developed for the synthesis of 2,3-dihydro-1*H*-xanthen-1-one derivatives (**61**) *via* the cycloaddition of 1,3-cyclohexanediones (**37b** or **37b′**) and salicylaldehyde (**44**) using glycine as promoter in [bmim]PF_6 at 25 °C (Scheme 23).[98] Conventional solvents, such as acetonitrile, DMF, DMSO, *etc.*, were also screened for this reaction but lower yields were attained. Under the optimized conditions, other amino acids, such as L-histidine, L-lysine, L-alanine, as catalyst produced lower yields. The [Bmim]PF_6 containing glycine was recovered and recycled four times without any loss in its catalytic activity.

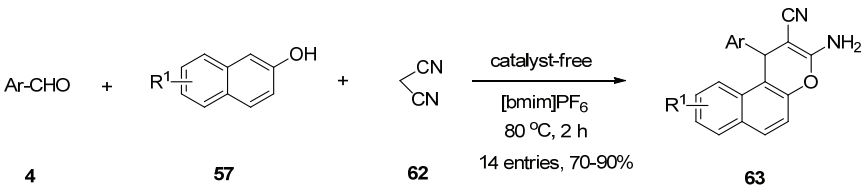


R = H or CH_3; R^1 = H, 3-Cl, 5-OCH_3

Scheme 23. [Bmim]PF_6-mediated glycine-catalysed synthesis of 2,3-dihydro-1*H*-xanthen-1-ones.

3.6. Synthesis of 2-amino-3-cyano-benzochromenes

2-Amino-3-cyano-pyrans and related derivatives possess immense biological activities.[99–101] A simple and facile protocol was developed for the efficient synthesis of 2-amino-3-cyano-benzochromenes (**63**) *via* one-pot three-component condensation between aromatic aldehydes (**4**), various substituted *β*-naphthols (**57**) and malononitrile (**62**) in [bmim]PF_6 at 80 °C (Scheme 24).[102]



R^1 = H
Ar = 4-Cl-C_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-ClC_6H_4, 3-$OCH_3C_6H_4$, C_6H_5, pyridyl

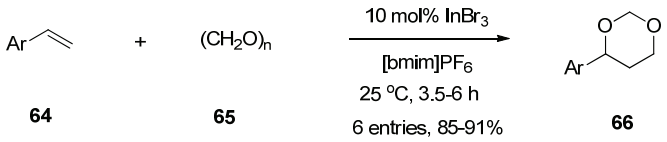
R^1 = 7-OCH_3
Ar = 4-Cl-C_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-Cl-C_6H_4, 3-$OCH_3C_6H_4$

Scheme 24. [Bmim]PF_6-mediated synthesis of 2-amino-3-cyano-benzochromenes.

Other ionic liquids, such as [bmim]Br, [bmim]BF_4, *n*-butylpyridinium bromide, cetylpyridinium chloride and *n*-butylpyridinium dodecyl sulphate, were also screened for this reaction but lower yields were attained. After completion of reaction, [bmim]PF_6 was successfully recovered and recycled several times. Some of the synthesized compounds possess prominent anti-proliferative activity. A range of aromatic aldehydes that include electron donating and withdrawing substituent are well tolerated under the optimized reaction conditions and produced excellent yields. Operational simplicity, high atom economy, excellent yields, catalyst-free reaction conditions are some of the major benefits of this developed protocol.

3.7. Synthesis of 1,3-dioxane derivatives

A series of 1,3-dioxane derivatives (**66**) was synthesized in excellent yields *via* the condensation of olefins (**64**) and paraformaldehyde (**65**) in the presence of a catalytic amount of $InBr_3$ in [bmim]PF_6 at 25 °C (Scheme 25).[103] The ionic liquid containing the catalyst was recovered and successfully recycled up to the fourth run with no appreciable loss in product formation.



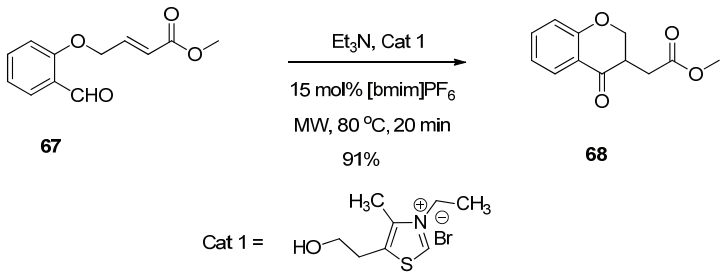
Ar = C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 1-naphthyl

Scheme 25. [Bmim]PF_6-mediated synthesis of 1,3-dioxane derivatives.

3.8. Synthesis of chromanone derivatives

A simple and facile microwave-assisted intramolecular Stetter reaction[104] was demonstrated with (*E*)-methyl 4-(2-formylphenoxy)but-2-enoate (**67**) to pre-

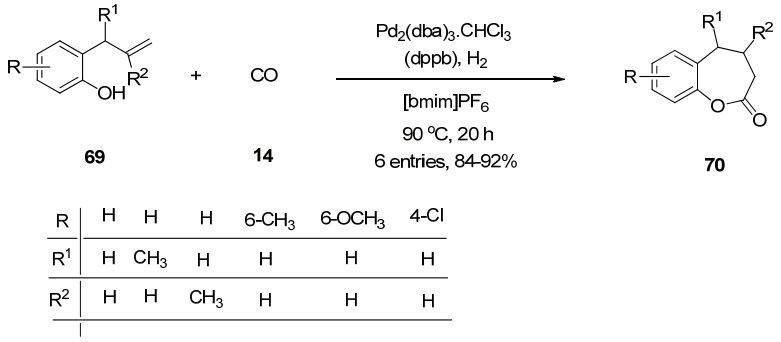
pare the corresponding chromanone derivatives (**68**). The reaction was realized under the catalytic combination of thiazolium salt and [bmim]PF_6 in basic medium at 80 °C (Scheme 26).[105] The ionic liquid containing catalyst was recovered and recycled several times.



Scheme 26. [Bmim]PF_6-catalyzed microwave-assisted synthesis of chromanone derivatives.

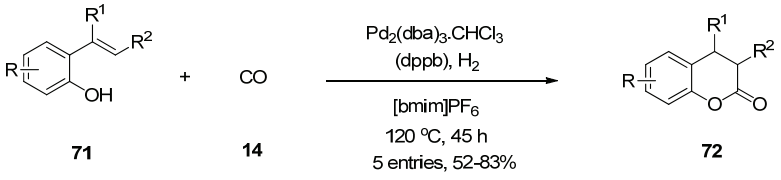
3.9. Synthesis of lactone and lactam derivatives

The ionic liquid [bmim]PF_6 was found to be an efficient reaction medium for the palladium-catalyzed cyclocarbonylation of 2-allylphenols (**69**, Scheme 27), 2-vinylphenols (**71**, Scheme 28), and 2-aminostyrenes (**73**, Scheme 29) using



R	H	H	H	6-CH_3	6-OCH_3	4-Cl
R^1	H	CH_3	H	H	H	H
R^2	H	H	CH_3	H	H	H

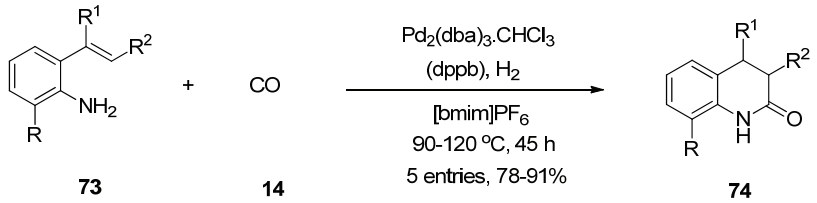
Scheme 27. [Bmim]PF_6-mediated synthesis of seven-membered lactones.



R	H	H	4-CH_3	4,6-diCl	H
R^1	H	CH_3	H	CH_3	H
R^2	H	H	H	H	CH_3

Scheme 28. [Bmim]PF_6-mediated synthesis of six membered-lactones.

carbon monoxide (**14**) to afford the corresponding lactones (**70** and **72**) or lactams (**74**), respectively, in good yields in the presence of 1,4-bis(diphenylphosphino)butane (dppb) as promoter at 90 °C. The ionic liquid containing the palladium catalyst and ligand was recovered and successfully recycled for several runs.[106]



R	H	H	H	OCH_3	OCH_3
R^1	H	CH_3	C_6H_5	CH_3	H
R^2	H	H	H	H	CH_3

Scheme 29. [Bmim]PF_6-mediated synthesis of six membered-lactams.

4. SYNTHESIS OF *N*,*O*-HETEROCYCLES

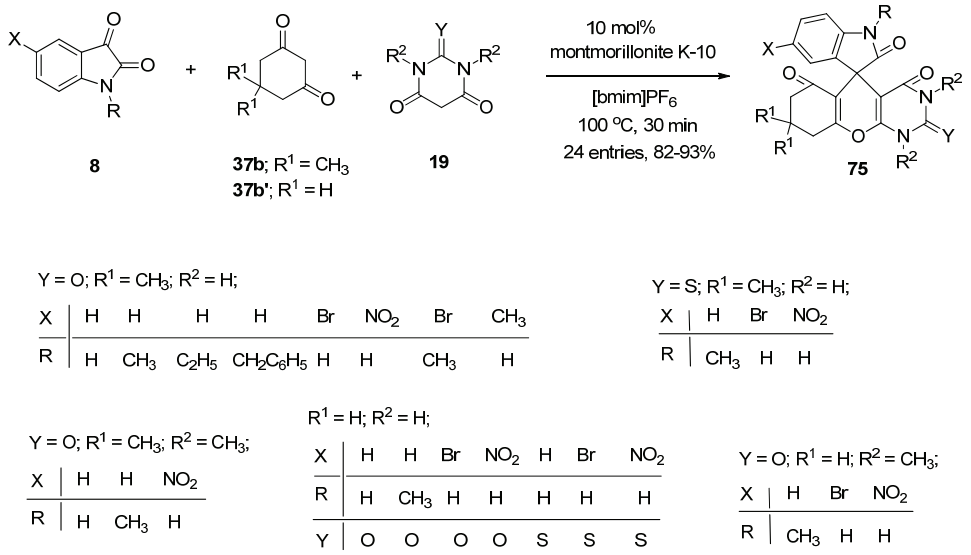
*4.1. Synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]tetraones*

A simple and facile protocol was developed for the efficient synthesis of a series of spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]tetraones (**75**) *via* one-pot three-component reactions of substituted isatins (**8**), dimedone (**37b**) and barbituric acid derivatives (**19**) in the presence of a catalytic amount of montmorillonite K-10 in [bmim]PF_6 at 100 °C (Scheme 30).[107]

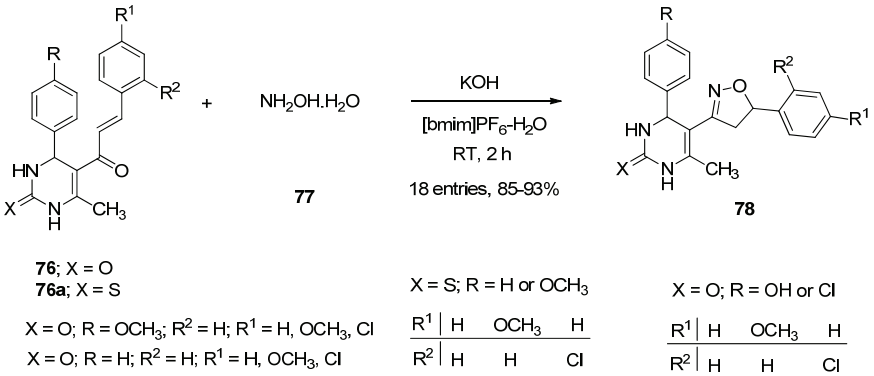
During optimization, [bmim]PF_6 was found to be superior to other butylmethylimidazolium-based ionic liquids, such as [bmim]BF_4, [bmim]Br, [bmim]CF_3COO and [bmim]Cl. Very short reaction times, a wide range of substrate tolerance, high atom economy, reusability of the media, excellent yields are some of the major advantages of this developed protocol.

4.2. Synthesis of pyrimidine containing isoxazolines

A series of pyrimidine-containing isoxazoline derivatives (**78**) was synthesized *via* the reactions of 3,4-dihydropyrimidin-2(1*H*)-ones (**76**) or 3,4-dihydro--2(1*H*)-pyrimidinethiones (**76a**) with hydroxylamine (**77**) using potassium hydroxide as a promoter in water–[bmim]PF_6 as a biphasic medium at ambient temperature. The reaction medium was successfully recovered and recycled ten times with no appreciable loss in yields (Scheme 31).[108] Short reaction times, a wide range of substrate tolerance, ambient conditions and good to excellent yields are some of the major benefits of this developed protocol.



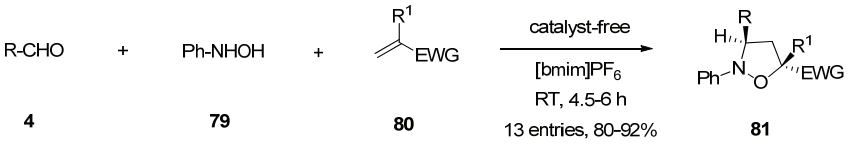
Scheme 30. [Bmim]PF_6-mediated synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline] derivatives.



Scheme 31. [Bmim]PF_6-mediated synthesis of pyrimidine-containing isoxazolines.

4.3. Synthesis of isoxazolidines

The ionic liquid [bmim]PF_6 was found to be an efficient medium for the 1,3--dipolar intermolecular cycloaddition of aldehydes (**4**), phenylhydroxylamine (**79**) and various electron deficient olefins (**80**) to afford the corresponding stereospecific isoxazolidines (**81**) under catalyst-free conditions at room temperature (Scheme 32).[109] Under the same reaction conditions, [bmim]BF_4 also afforded the same products with comparable yields. A catalyst-free reaction, a wide range of substrate tolerance, high atom economy, operational simplicity and good to excellent yields are some of the advantages of this protocol.



EWG = electron withdrawing group

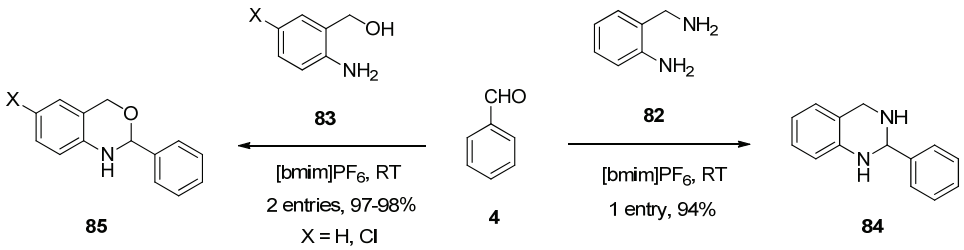
EWG	CN	$COCH_3$	CN	CN	$COOCH_3$	CN	CN	$COOCH_3$
R	C_6H_5	C_6H_5	C_6H_5CH=CH	2-furyl	4-ClC_6H_4	3,4-diClC_6H_3	3-ClC_6H_4	3-$NO_2C_6H_4$
R^1	H	H	H	H	CH_3	H	H	CH_3

EWG	CN	$COCH_3$	CN	$COOCH_3$	$COOCH_3$
R	3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	3,4-OCH_2O-C_6H_3	4-$OCH_3C_6H_4$	C_6H_5
R^1	H	H	H	CH_3	H

Scheme 32. [Bmim]PF_6-mediated synthesis of isoxazolidines at room temperature.

4.4. Synthesis of benzoxazine and quinazoline

The ionic liquid [bmim]PF_6 was found to be a safe and recyclable reaction medium for the efficient synthesis of 1,2,3,4-tetrahydro-2-phenylquinazoline (**84**) and 1,4-dihydro-2-phenyl-2*H*-3,1-benzoxazines (**85**) from the reaction of benzaldehyde (**4**) and 2-aminobenzyl amine (**82**) or 2-aminobenzyl alcohols (**83**), respectively, at room temperature (Scheme 33).[110]

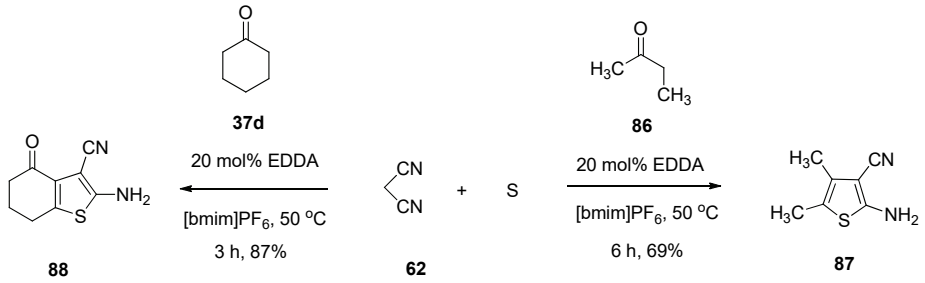


Scheme 33. [Bmim]PF_6-mediated synthesis of benzoxazine and quinazoline at room temperature.

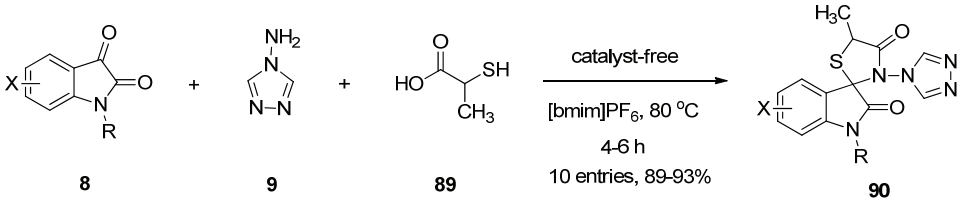
5. SYNTHESIS OF *S*-HETEROCYCLES

5.1. Synthesis of 2-aminothiophenes

Hu *et al.*[111] demonstrated the ionic liquid [bmim]PF_6-mediated Gewald synthesis[112] to afford the corresponding 2-aminothiophenes (**87** and **88**) starting from various carbonyl compounds (**37d** and **86**), malononitrile (**62**) and sulphur in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA) at 50 °C. After completion of the reaction, the ionic liquid containing catalyst was recovered and reused several times without any loss in its activity (Scheme 34).



Scheme 34. [Bmim]PF_6-mediated synthesis of 2-aminothiophenes.



X = H; R = H, $COCH_3$, CH_3, CH_2NEt_2, CH_2NMe_2, $CH_2C_6H_5$, piperidin-1-ylmehyl

X	5-Cl	5-F	5-Cl
R	H	H	CH_3

Scheme 35. [Bmim]PF_6-mediated synthesis of spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)--diones.

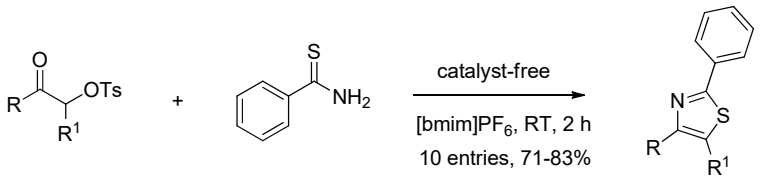
6. SYNTHESIS OF *N*,*S*-HETEROCYCLES

*6.1. Synthesis of spiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones*

A simple, facile and environmentally sustainable protocol was developed for the synthesis of novel spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-dione derivatives (**90**) *via* the one-pot three-component condensation of isatins (**8**), 4-amino-4*H*-1,2,4-triazole (**9**) and 2-sulfanylpropanoic acid (**89**) under catalyst--free conditions in [bmim]PF_6 at 80 °C (Scheme 35).[113] Catalyst-free reaction conditions, high atom economy, good to excellent yields are some of the major benefits of this method.

6.2. Synthesis of 2-phenylthiazoles

A series of 2-phenylthiazoles (**93**) was synthesized *via* the cycloaddition of α-tosyloxyketones (**91**) and thiobenzamide (**92**) in [bmim]PF_6 as an efficient and reusable ionic liquid under catalyst-free conditions at room temperature (Scheme 36).[114] Catalyst-free ambient reaction conditions, operational simplicity, good yields are some of the advantages of this method. After completion of the react-ion, the ionic liquid was successfully recovered and reused without any loss in its activity.



91 **92** **93**

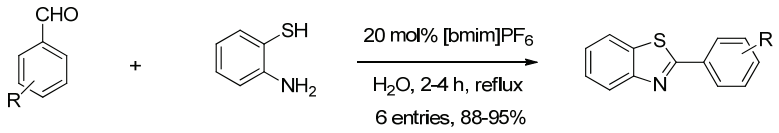
R^1 = H;
R = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-furyl, 3-thienyl

R^1 = $COOC_2H_5$; R = C_6H_5, CH_3, OC_2H_5

Scheme 36. [Bmim]PF_6-mediated synthesis of 2-phenylthiazoles at room temperature.

6.3. Synthesis of benzothiazole derivatives

[Bmim]PF_6 efficiently catalyzed the reaction of various aldehydes (**4**) and 2-aminothiophenol (**94**) to afford the corresponding benzothiazoles (**95**) in aqueous media under reflux conditions (Scheme 37).[115]



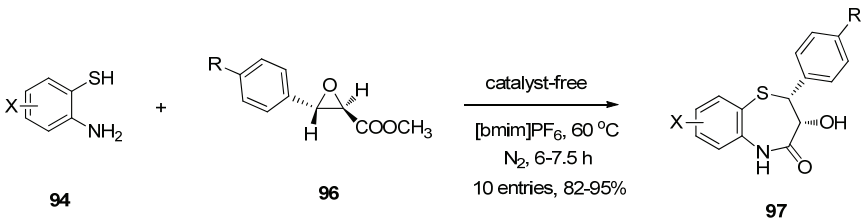
4 **94** **95**

R = H, 4-OH, 4-OCH_3, 4-Cl, 4-Br, 4-CH_3

Scheme 37. [Bmim]PF_6-catalyzed synthesis of benzothiazole derivatives.

6.4. Synthesis of 1,5-benzothiazepine-4-ones

A facile and convenient protocol was developed for the regioselective synthesis of a series of 1,5-benzothiazepin-4-one derivatives (**97**) starting from substituted 2-aminobenzenethiol (**94**) and methyl (±)-*trans*-3-(4-methoxy/(benzyloxy)phenyl)--glycidate (**96**) in [bmim]PF_6 under catalyst-free conditions at 60 °C (Scheme 38).[116]



94 **96** **97**

R = OCH_3; X = H, 7-Cl, 8-Cl, 9-Cl, 9-F, 7-CF_3

R = $OCH_2C_6H_5$; X = H, 7-Cl, 8-Cl, 7-CF_3

Scheme 38. [Bmim]PF_6-mediated synthesis of 1,5-benzothiazepine-4-ones.

Catalyst-free reaction conditions, operational simplicity, reusability of media and good to excellent yields are some of the major advantages of this developed protocol.

7. CONCLUSIONS

The ionic liquid [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) has been successfully employed as an efficient, commercially available, cheap, low toxicity and recyclable reaction medium for various organic transformations. During optimization, on many occasions, it was found that the efficiency of [bmim]PF_6 was better than those of other imidazolium-based ionic liquids, such as [bmim]BF_4, [bmim]OH, [bmim]Br, [bmim]Cl, [bmim]ClO_4, [bmim]CH_3COO, [bmim]NTf_2, [bmim]N_3, [bmim]$AlCl_4$, *etc*. In many situations, the addition of another catalyst was not required for the [bmim]PF_6--mediated transformations. The weak electrostatic interactions of hexafluorophosphate with the imidazolium cation provide good thermal and electrochemical stability of [bmim]PF_6. Other favourable physical and chemical properties, such as mild properties, low volatility, lack of inflammability, commercial availability and excellent solubility with many organic compounds make this ionic liquid superior. After completion of the reaction, in the majority of cases, the ionic liquid was successfully recovered and recycled several times without significant loss in its efficacy. The present review summarizes the applications of [bmim]PF_6 as an efficient, cheap, commercially available and reusable ionic liquid for the hitherto reported synthesis of structurally diverse bioactive heterocycles.

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ИЗВОД

[bmim]PF_6: ЕФИКАСАН МЕДИЈУМ ЗА СИНТЕЗУ РАЗЛИЧИТИХ БИОАКТИВНИХ ХЕТЕРОЦИКЛИЧНИХ ЈЕДИЊЕЊА

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Хетероцикли су од изузетне важности због тога што чине важне структурне елементе многих лекова присутних на тржишту. Истовремено, у последњој деценији забележен је изузетан пораст у примени јонске течности [bmim]PF_6 (1-бутил-3-метил-1*H*-имидазолијум хексафлуорофосфат) као ефикасног, јефтиног, комерцијално доступног и мање токсичног реакционог медијума за различите трансформације у органској хемији. Овај прегледни чланак даје приказ најновије примене [bmim]PF_6 као ефикасног реакционог медијума за синтезу различитих биолошки важних хетероцикличних једињења.

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