

Green Chemistry Letters and Reviews

ISSN: 1751-8253 (Print) 1751-7192 (Online) Journal homepage: http://www.tandfonline.com/loi/tgcl20

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To cite this article: Rajanarendar Eligeti , Govrardhan Reddy Kundur , Sivarami Reddy Atthunuri & Nagi Reddy Modugu (2012) Brønsted acidic ionic liquid [HMIm]BF_4 promoted simple and efficient one-pot green synthesis of isoxazolyl-1,3-benzoxazines at ambient temperature, Green Chemistry Letters and Reviews, 5:4, 699-705, DOI: 10.1080/17518253.2012.700736

To link to this article: https://doi.org/10.1080/17518253.2012.700736

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Published online: 28 Aug 2012.

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Green Chemistry Letters and Reviews
Vol. 5, No. 4, December 2012, 699–705

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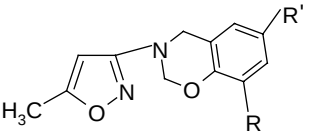
Brønsted acidic ionic liquid [HMIm]BF_4 promoted simple and efficient one-pot green synthesis of isoxazolyl-1,3-benzoxazines at ambient temperature

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(Received 21 January 2011; final version received 16 May 2012)

Brønsted acidic ionic liquid [HMIm]BF_4 has been used as a nonvolatile, ecofriendly solvent, and catalytic medium for the one-pot green synthesis of isoxazolyl-1,3-benzoxazines. The reaction afforded excellent yield in short reaction time, and avoids multistep synthesis. The easy of recyclability of the IL makes the reaction economically and potentially viable for commercial applications.



Keywords: Brønsted acidic ionic liquid [HMIm]BF_4; one-pot synthesis; isoxazolyl-1,3-benzoxazines; recyclability; ecofriendly

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Introduction

Environment protection laws and corporate pressure to minimize the amount of toxic waste arising from chemical syntheses have motivated the development of innovative and eco-friendly chemical technologies. In this context, room temperature ionic liquids, especially those based on 1-methyl imidazolium cation, have given a promise as attractive alternative to conventional solvents (*1, 2*). They are referred to as *designer solvents* as their properties can be fine-tuned by changing the anion or the alkyl group attached to the cation. Their high polarity and ability to solubilize both organic and inorganic compounds can result in enhanced rate of chemical transformations and they can provide higher selectivities compared to conventional solvents. The use of room temperature ionic liquids has made significant advancement in the development of clean chemical processes in organic synthesis targeted to avoid or at least minimize the use of toxic or waste generating reagents or solvents. Because of their distinct advantages, ionic liquids can make a great contribution to green chemistry. The potential of ionic liquid (IL) as green solvent has already been established in several chemical transformations (*3, 4*). The dual role of Brønsted acidic ionic liquid [HMIm]BF_4 as green solvent and catalyst was proved in a variety of organic chemical reactions (*5–7*). The involvement of ionic liquid as a catalyst in the mechanism was also described (*8–11*). Recently, Reddy et al. (*12*) reported the reductive amination of carbonyl compounds using $NaBH_4$ in a [HMIm]BF_4 ionic liquid.

1,3-Benzoxazines constitute an important class of heterocycles that have been explored for developing pharmaceuticals due to their wide variety of pharmacological activity (*13–15*). Even though 1,3-benzoxazines are synthesized by different multistep methods (*16–19*), one of the most important method within this is, condensation of aldehydes with amines, followed by reduction, and finally by cyclization with formaldehyde (*20, 21*). These reactions are being conducted in conventional solvents such as alcohol. However, this method involves multistep synthesis, and the use of excess amount of amine and formaldehyde or hazardous organic solvents, tedious work-up, and refluxing with hot solvents for longer periods. These may not be the preferred choices in the view of the green chemistry. Hence, an efficient and mild synthesis is needed for contemporary chemical synthesis of 1,3-benzoxazines. In our continuing efforts to utilize ionic liquids as environmentally attractive

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ISSN 1751-8253 print/ISSN 1751-7192 online
© 2012 Rajanarendar Eligeti, Govrardhan Reddy Kundur, Sivarami Reddy Atthunuri and Nagi Reddy Modugu
http://dx.doi.org/10.1080/17518253.2012.700736
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media, for the synthesis and catalytic processes, we have some interest in the synthesis of different heterocycles carrying isoxazole moiety (*22–26*). As a sequel to our investigations on multicomponent synthesis (*27–30*), as well as green synthesis, we, herein, report for the first time a simple and efficient one-pot synthesis of isoxazolyl 1,3-benzoxazines promoted by the Brønsted acidic IL, 1-methyl imidazolium tetraflouroborate [HMIm]BF_4, as a solvent and catalyst, under mild conditions. The nonvolatile IL can be efficiently recovered and reused, and the process does not require any additional catalyst. Literature survey revealed that even though ILs are being extensively used in heterocyclic synthesis (*31*), only a single instance is available for the synthesis of 1,3-benzoxazines by using IL (*32*). But, this method does not involve a one-pot synthesis. In view of this, our method has a merit, where by the title compounds are being synthesized in a one-pot green method under mild conditions at ambient temperature in excellent isolated yields in short reaction time.

Results and discussion

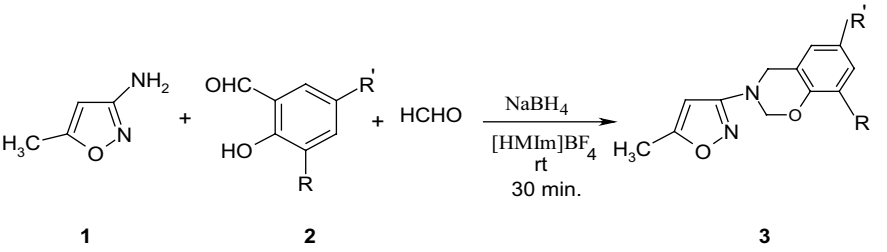
In view of the emerging importance of the ionic liquids as a novel reaction media and catalyst, we, herein, report one-pot synthesis of isoxazolyl-1,3-benzoxazine derivatives in ionic liquids. Initial experimentation was undertaken in Brønsted acidic ionic liquid, 1-methyl-imidazolum tetrafluoro borate, [HMIm]BF_4. Treatment of salicylaldehyde **2a** with 3-amino-5-methylisoxazole **1** in the presence of IL [HMIm]BF_4 for 10 min followed by the addition of $NaBH_4$ and continuing the reaction for another 10 min, and finally the addition of HCHO with stirring at ambient temperature for 10 min afforded the 3-(5-methyl-3-isoxazolyl)-3,4-dihydro-*2H*-1,3-benzoxazine **3a** in 95% yield (Scheme 1).

A variety of salicylaldehyde derivatives reacted smoothly with isoxazole amine, HCHO in the presence of IL [HMIm]BF_4 and $NaBH_4$ under similar reaction conditions to give the corresponding isoxazolyl-2*H*-1,3-benzoxazines **(3b–g)** in excellent yields (90–95%). In all the cases, the reaction proceeded efficiently at room temperature with excellent yields in short reaction time (30 min)(Table 1).

To determine whether the ionic liquid [HMIm]BF_4, was an essential factor to realize the conversion of this reaction, the same reaction was carried out in CH_2Cl_2, CH_3CN and ethanol in the absence of ionic liquid. The reaction did not proceed at all in the absence of IL. To know the influence of Brønsted acidic IL [HMIm]BF_4 in this reaction, the reaction was also carried out with other ionic liquids such as [bmIm]BF_4, [bmIm]Br, [bmIm]OH. In these reactions, the reaction is sluggish and the conversion only reached 40–65%, and the reaction required more time (1.5–4 h) (Table 2). It is noteworthy that [HMIm]BF_4 is highly influencing the reaction by acting as Brønsted acid catalyst as well as effective solvent media for the synthesis of title compounds.

Having established that, the best solvent and catalyst is [HMIm]BF_4 for this transformation, another advantage is, it can be easily recovered after the completion of the reaction and can be reused in subsequent runs (five runs) without much loss of efficiency and with negligible loss of the IL (Table 3). The products were easily separated by simple extraction with ether and characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy and also by analytical data.

Having these results in hand, we investigated the evidence for the formation of isoxazolyl-1,3-benzoxazines, by conducting the reaction in a multistep synthesis. We reacted salicylaldehyde **2a** with 3-amino-5-methylisoxazole **1** in refluxing alcohol for 2 h, which led to the formation of Schiff base **4a** by condensation. Compound **4a** was later reduced with $NaBH_4$ in ethanol, by stirring the reaction mixture for 30 min at room temperature, to afford the compound **5a**. Finally, compound **5a** was cyclized to title compound **3a** by heating with HCHO on hot water bath for 5 h. Similarly, the derivatives of isoxazolyl-1,3-benxozines **3b–3g** have been prepared by multistep synthesis, adopting the same procedure (Scheme 2). In all the cases, the reaction afforded 60–70% yield in this method. The compounds **3a–3g**, obtained in a multistep synthesis, were found to be



Scheme 1. One-pot synthesis of isoxazolyl 1,3-benzoxazines in IL.

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Table 1. Synthesis of isoxazolyl-1,3-benzoxazines **3a–g** in IL [HMIm]BF_4.

Entry	Compound	R	R'	Time (h)	Yield (%)	Melting point (°C)
1	3a	H	H	0.5	95	108–110
2	3b	H	Cl	0.5	96	123–126
3	3c	Cl	Cl	0.5	95	132–135
4	3d	H	Br	0.5	98	137–140
5	3e	Br	Br	0.5	97	144–147
6	3f	H	CH_3	1.0	98	126–128
7	3g	H	OCH_3	1.0	91	131–133

similar to that of one-pot green synthesis from M.Ps, IR, ^{1}H NMR, ^{13}C NMR, and mass spectra and by microanalytical data. On the whole, in a multistep synthesis, the reaction required 7.5 h time, excess of amine and HCHO, and the yield in the reduction step is not satisfactory. From a recent atom-economical stand point, the use of nearly equimolar amounts of substrate is strongly required. It is evident that our methodology utilizing IL as solvent and catalyst is reasonably good, because it does not involve so many isolations required for multistep synthesis, and the reaction time is drastically reduced from 7.5 h to 30 min, and the product yields are excellent, and involves a simple method. To the best of our knowledge, this report is the first of its kind to construct isoxazolyl-1,3-benzoxazines exploring IL as solvent and catalyst.

Experimental

Commercial grade reagents were used as supplied. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on the pre-coated silica gel F_{254} plates from Merck and visualization was done by exposing to the iodine vapor. All the melting points were determined on a Fischer-Johns apparatus and are uncorrected. IR spectra were recorded on KBr discs on a Perkin–Elmer Bx series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded as a Varian Gemini 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were determined by a Perkin–Elmer 240 CHN elemental analyzer.

Table 2. Optimization of reaction conditions by using different ILs.

Entry	IL	Time (h)	Yield (%)[a]
1	[HMIm]BF_4	0.5	95
2	[bmIm] BF_4	1.5	65
3	[bmIm]Br	2.5	60
4	[bmIm]OH	4.0	40
5	–	4.0	–

[a]The reaction did not proceed in the absence of IL.

Table 3. Recycling of IL [HMIm]BF_4.

Run IL recycled (in ml)	Yield (%)
1–5	95
2–4.8	94
3–4.5	94
4–4.2	93
5–4.0	92

The ILs [HMIm]BF_4, [bmIm]BF_4, [bmIm]Br, [bmIm]OH were prepared according to the reported procedures (5, *33–35*).

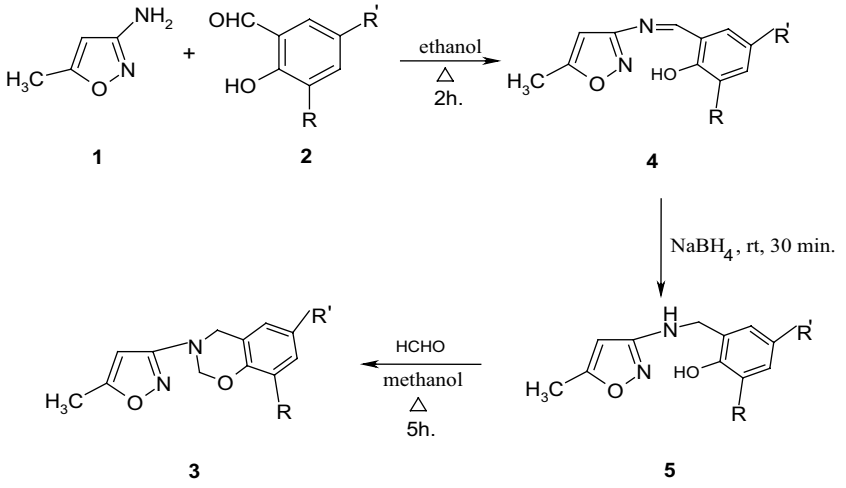
General procedure for the synthesis of isoxazolyl -1,3-benzoxazines (3a–g)

To 3-amino-5-methylisoxazole **1** (1mmol) in IL, [HMIm]BF_4 (5ml), salicyladehyde **2** (1mmol) was added and the reaction mixture stirred at room temperature for 10 min, followed by the addition of $NaBH_4$ (2 mmol) and the stirring continued for another 10 min, finally, formalin (37%, 1 ml) was added to it, and the reaction continued for another 10 min. The reaction was monitored by TLC form time to time. After completion of the reaction, the reaction mixture was extracted with diethyl ether. The combined extracts were concentrated under reduced pressure and the resulting product was directly charged on to a small silica gel column and eluted with a mixture of benzene-ethyl acetate (1:1) to afford pure 1,3-benzoxazine. The IL was solubilized in CH_3CN and filtered to separate $NaBH_4$ and the organic layer was evaporated and the IL dried under vacuum and recycled in subsequent reactions (five runs).

Spectral data of synthesized compounds

3-(5-Methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3a**)

IR (KBr) cm^{-1}: 2990, 2930; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.3 (s, 3*H*, CH_3), 4.6 (s, 2*H*, CH_2N), 5.2 (s, 2*H*, CH_2O), 5.8 (s, 1*H*, isoxazole-H), 6.8–7.2 (m, 4*H*, Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.18 (C-6″), 43.65 (C-4), 93.28 (C-2), 116.75 (C-4″), 119.59 (Ar-C), 125.43 (Ar-C), 128.65 (Ar-C), 130.07 (Ar-C), 135.43 (Ar-C), 155.28 (C-3″), 164.45 (C-5″), 168.42 (C-8′); MS (EI): *m*/*z* 217 $(M + H)^+$. Analysis calculated for



Scheme 2. Multistep synthesis of isoxazolyl 1,3-benzoxazines in conventional solvent.

$C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.66; H, 5.54; N, 12.93%.

6-Chloro-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3b**)
IR (KBr) cm^{-1}: 2980, 2935; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.2 (s, 3*H*, CH_3), 4.4 (s, 2*H*, CH_2N), 5.2 (s, 2*H*, CH_2O), 5.9 (s, 1*H*, isoxazole-H), 6.9–7.2 (m, 3*H*, Ar-H); MS (EI): *m*/*z* 251 $(M + H)^+$. Analysis calculated for $C_{12}H_{11}N_2O_2Cl$:C, 57.49; H, 4.42; N, 11.10. Found: C, 57.60; H, 4.40; N, 11.20%.

6,8-Dichloro-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3c**)
IR (KBr) cm^{-1}: 2995, 2935; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.3 (s, 3*H*, CH_3), 4.5 (s, 2*H*, CH_2N), 5.1 (s, 2*H*, CH_2O), 6.0 (s, 1*H*, isoxazole-H), 7.0 (s, 1*H*, Ar-H), 7.3 (s, 1*H*, Ar-H); MS (EI): *m*/*z* 285 $(M + H)^+$. Analysis calculated for $C_{12}H_{10}N_2O_2Cl_2$: C, 50.55; H, 3.54; N, 9.82. Found: C, 50.72; H, 3.52; N, 9.85%.

6-Bromo-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3d**)
IR (KBr) cm^{-1}: 2990, 2935; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.2 (s, 3*H*, CH_3), 4.3 (s, 2*H*, CH_2N), 5.0 (s, 2*H*, CH_2O), 6.0 (s, 1*H*, isoxazole-H), 6.9–7.3 (m, 3*H*, Ar-H); MS (EI): *m*/*z* 295 $(M + H)^+$. Analysis calculated for $C_{12}H_{11}N_2O_2Br$: C, 48.84; H, 3.76; N, 9.49. Found: C, 48.97; H, 3.74; N, 9.52%.

6,8-Dibromo-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3e**)
IR (KBr) cm^{-1}: 2995, 2940; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.3 (s, 3*H*, CH_3), 4.6 (s, 2*H*, CH_2N), 5.3 (s, 2*H*, CH_2O), 6.0 (s, 1*H*, isoxazole-H), 7.3 (s, 1*H*, Ar-H), 7.5 (s, 1*H*, Ar-H); MS (EI): *m*/*z* 373 $(M + H)^+$. Analysis calculated for $C_{12}H_{10}N_2O_2Br_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.70; H, 2.68; N, 7.55%.

6-Methyl-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3f**)
IR (KBr) cm^{-1}: 2995, 2925; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.2 (s, 3*H*, CH_3), 2.5 (s, 3*H*,Ar-CH_3), 4.5 (s, 2*H*, CH_2N), 5.1 (s, 2*H*, CH_2O), 5.9 (s, 1*H*, isoxazole-H), 6.9–7.3 (m, 3*H*, Ar-H); MS (EI): *m*/*z* 231 $(M + H)^+$. Analysis calculated for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.79; H, 6.11; N, 12.20%.

6-Methoxy-3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazine (**3g**)
IR (KBr) cm^{-1}: 2990, 2930; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.3 (s, 3*H*, CH_3), 3.8 (s, 3*H*,OCH_3), 4.5 (s, 2*H*, CH_2N), 5.2 (s, 2*H*, CH_2O), 6.0 (s, 1*H*, isoxazole-H), 6.8–7.2 (m, 3*H*, Ar-H); MS (EI): *m*/*z* 247 $(M + H)^+$. Analysis calculated for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.45; H, 5.72; N, 11.35%.

Procedure for the multistep synthesis of isoxazolyl-1,3-benzoxazines in conventional solvent

(a) *2-[(5-Methyl-3-isoxazolyl)imino]methyl phenols* (***4a–g***)*:* A mixture of 3-amino-5-methylisoxazole **1** (2 mmol) and salicylaldehyde **2**(1 mmol) were refluxed in ethanol (10 ml) for 2 h. The reaction is monitored by TLC. After completion of the reaction, the reaction mixture was cooled, and the solid that separated was filtered and recrystallized from pet-ether.

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2-[(5-Methyl-3-isoxazolyl)imino]methyl phenol **(4a)**
Melting point 55–57°C; yield 60%; IR (KBr) cm^{-1}: 3400, 1607, 1577, 1400, 1282, 755; ^1H NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 3*H*, CH_3), 6.0 (s, 1*H*, isoxazole-H), 6.8–7.5 (m, 4*H*, Ar-H), 8.8 (s, 1*H*, –N = CH–), 12.4 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 203 $(M + H)^+$. Analysis calculated for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.93; N, 13.85. Found: C, 65.33; H, 4.88; N, 13.86%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4-chlorophenol **(4b)**
Melting point 90–93°C; yield 65%;IR (KBr) cm^{-1}: 3415, 1600, 1560, 1395, 1290, 750; ^1H NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH_3), 6.2 (s, 1*H*, isoxazole-H), 6.5–7.6 (m, 3*H*, Ar-H), 8.5 (s, 1*H*, –N = CH–), 12.0 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 237 $(M + H)^+$. Analysis calculated for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.89; H, 3.81; N, 11.86%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4,6-dichlorophenol **(4c)**
Melting point 121–123°C; yield 60%;IR (KBr) cm^{-1}: 3410, 1610, 1570, 1400, 1280, 755; ^1H NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 3*H*, CH_3), 6.0 (s, 1*H*, isoxazole-H), 7.1 (s, 1*H*,Ar-H), 7.5 (s, 1*H*, Ar-H), 8.6 (s, 1*H*, –N = CH–), 12.2 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 271 $(M + H)^+$. Analysis calculated for $C_{11}H_8N_2O_2Cl_2$: C, 48.73; H, 2.97; N, 10.33. Found: C, 48.78; H, 2.96; N, 10.37%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4-bromophenol **(4d)**
Melting point 109–112°C; yield 65%;IR (KBr) cm^{-1}: 3400, 1610, 1575, 1410, 1275, 760; ^1H NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH_3), 6.1 (s, 1*H*, isoxazole-H), 6.8–7.8 (m, 4*H*, Ar-H), 8.6 (s, 1*H*, –N = CH–), 12.5 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 281 $(M + H)^+$. Analysis calculated for $C_{11}H_9N_2O_2Br$: C, 47.00; H, 3.23; N, 9.97. Found: C, 47.04; H, 3.21; N, 10.00%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4,6-dibromophenol **(4e)**
Melting point 128–130°C; yield 65%;IR (KBr) cm^{-1}: 3410, 1600, 1565, 1290, 740; ^1H NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 3*H*, CH_3), 6.1 (s, 1*H*, isoxazole-H), 7.2 (s, 1*H*, Ar-H), 7.6 (s, 1*H*, Ar-H), 8.6 (s, 1*H*, –N = CH–), 12.0 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 359 $(M + H)^+$. Analysis calculated for $C_{11}H_8N_2O_2Br_2$: C, 36.70; H, 2.24; N, 7.78. Found: C, 36.77; H, 2.23; N, 7.82%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4-methylphenol **(4f)**
Melting point 75–77°C; yield 60%;IR (KBr) cm^{-1}: 3400, 1615, 1575, 1275, 744; ^1H NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH_3), 2.5(s, 3*H*, Ar-CH_3), 6.2 (s, 1*H*, isoxazole-H), 6.5–7.4 (m, 3*H*, Ar-H), 8.5 (s, 1*H*, –N = CH–), 12.2 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 217 $(M + H)^+$. Analysis calculated for $C_{12}H_{12}N_2O_2$: C, 66.55; H, 5.59; N, 12.95. Found: C, 66.60; H, 5.55; N, 12.90%.

2-((Z)-(5-methylisoxazol-3-ylimino)methyl)-4-methoxyphenol **(4g)**
Melting point 100–102°C; yield 65%;IR (KBr) cm^{-1}: 3420, 1620, 1580, 1279, 755; ^1H NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH_3), 3.8 (s, 3*H*, OCH_3), 6.2 (s, 1*H*, isoxazole-H), 6.6–7.6 (m, 3*H*, Ar-H), 8.4 (s, 1*H*, –N = CH–), 12.0 (s, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 233 $(M + H)^+$. Analysis calculated for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.10; H, 5.25; N, 12.09%.

(b) *2-[(5-Methyl-3-isoxazolyl)amino]methyl phenol (**5a–g**):* Sodium borohydride (2 mmol) was added to solution of the compound **4** (1 mmol) in methanol (10 ml) and mixture was stirred for 30 min at room temperature. The reaction is monitored by TLC. The solid separated on pouring the reaction mixture into ice-cold water was filtered and recrystallized from ethanol.

2-[(5-Methyl-3-isoxazolyl)amino]methyl phenol **(5a)**
Melting point 83–85°C; yield 65%; IR (KBr) cm^{-1}: 3640, 3376, 1631, 1458, 826, 756; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.2 (s, 3*H*, CH_3), 4.3 (s, 2*H*, –N–CH_2–), 5.2 (bs, 1*H*, NH, D_2O exchangeable), 5.6 (s, 1*H*, isoxazole-H), 6.8–7.2 (m, 4*H*, Ar-H), 9.4 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 205 $(M + H)^+$; Analysis calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.70; H, 5.80; N, 13.72%.

2-((5-methylisoxazol-3-ylamino)methyl)-4-chlorophenol **(5b)**
Melting point 100–103°C; yield 60%; IR (KBr) cm^{-1}: 3645, 3370, 1625, 1455, 830, 760; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.4 (s, 3*H*, CH_3), 4.2 (s, 2*H*, –N–CH_2–), 5.0 (bs, 1*H*, NH, D_2O exchangeable), 6.0 (s, 1*H*, isoxazole-H), 6.5–7.2 (m, 4*H*, Ar-H), 9.6 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m/z* 239 $(M + H)^+$; Analysis calculated for $C_{11}H_{11}N_2O_2Cl$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.40; H, 4.62; N, 11.76%.

2-((5-methylisoxazol-3-ylamino)methyl)-4,6-dichlorophenol (**5c**)
Melting point 111–113°C; yield 65%; IR (KBr) cm^{-1}: 3640, 3380, 1635, 1450, 810, 755; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.4 (s, 3*H*, CH_3), 4.0 (s, 2*H*, –N–CH_2–), 5.4 (bs, 1*H*, NH, D_2O exchangeable), 6.2 (s, 1*H*, isoxazole-H), 7.3 (s, 1*H*, Ar-H), 7.7 (s, 1*H*, Ar-H) 9.8 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m*/*z* 273 $(M + H)^+$; analysis calculated for $C_{11}H_{10}N_2O_2Cl_2$: C, 48.38; H, 3.69; N, 10.26. Found: C, 48.42; H, 3.67; N, 10.29%.

2-((5-methylisoxazol-3-ylamino)methyl)-4-bromophenol (**5d**)
Melting point 117–119°C; yield 60%; IR (KBr) cm^{-1}: 3645, 3380, 1625, 1450, 830, 755; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.3 (s, 3*H*, CH_3), 4.2 (s, 2*H*, –N–CH_2–), 5.2 (bs, 1*H*, NH, D_2O exchangeable), 6.1 (s, 1*H*, isoxazole-H), 6.6–7.5 (m, 4*H*, Ar-H), 9.6 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m*/*z* 283 $(M + H)^+$; analysis calculated for $C_{11}H_{11}N_2O_2Br$: C, 46.67; H, 3.92; N, 9.89. Found: C, 46.70; H, 3.90; N, 9.92%.

2-((5-methylisoxazol-3-ylamino)methyl)-4,6-dibromophenol (**5e**)
Melting point 134–137°C; yield 65%; IR (KBr) cm^{-1}: 3630, 3360, 1625, 1445, 810, 770; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.3 (s, 3*H*, CH_3), 4.0 (s, 2*H*, –N–CH_2–), 5.4 (bs, 1*H*, NH, D_2O exchangeable), 6.1 (s, 1*H*, isoxazole-H), 7.3 (s, 1*H*, Ar-H), 7.6 (s, 1*H*, Ar-H) 9.7 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m*/*z* 361 $(M + H)^+$; analysis calculated for $C_{11}H_{10}N_2O_2Br_2$: C, 36.50; H, 2.78; N, 7.74. Found: C, 36.56; H, 2.77; N, 7.77%.

2-((5-methylisoxazol-3-ylamino)methyl)-4-methylphenol (**5f**)
Melting point 90–95°C; yield 60%; IR (KBr) cm^{-1}: 3640, 3375, 1620, 1440, 830, 760; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.3 (s, 3*H*, CH_3), 2.5(s, 3*H*, Ar-CH_3), 4.1 (s, 2*H*, –N–CH_2–), 5.1 (bs, 1*H*, NH, D_2O exchangeable), 6.0 (s, 1*H*, isoxazole-H), 6.7–7.9 (m, 3*H*, Ar-H), 9.8 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m*/*z* 219 $(M + H)^+$; analysis calculated for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.09; H, 6.50; N, 12.90%.

2-((5-methylisoxazol-3-ylamino)methyl)-4-methoxyphenol (**5g**)
Melting point 115–117°C; yield 65%; IR (KBr) cm^{-1}: 3635, 3365, 1635, 1450, 840, 780; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.3 (s, 3*H*, CH_3), 3.7 (s, 3*H*, OCH_3), 4.4 (s, 2*H*, –N–CH_2–), 5.1 (bs, 1*H*, NH, D_2O exchangeable), 6.0 (s, 1*H*, isoxazole-H), 6.7–7.8 (m, 3*H*, Ar-H), 9.3 (bs, 1*H*, OH, D_2O exchangeable). MS (EI): *m*/*z* 235 $(M + H)^+$; analysis calculated for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.58; H, 6.00; N, 11.90%.

(c) *3-(5-Methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazines* (***3a–g***): Compound **5** (1 mmol) and formalin (37%, 1 ml) were refluxed on a hot water bath for 5 h in methanol (10 ml). After completion of the reaction (monitored by TLC), solvent was removed under vacuum and the crude product obtained was recrystallized from ethanol. The reaction afforded the products in 60–70% yield. The spectral data of the compounds (**3a–g**) obtained in this method is identical to that of compound (**3a–g**), obtained in a one-pot green synthesis by using IL.

Conclusion

This article describes a simple and efficient method for the green synthesis of isoxazolyl-1,3-benzoxazine derivatives through multicomponent one-pot protocol in a Brønsted acidic ionic liquid $[HMIm]BF_4$ as a novel solvent and catalytic system using inexpensive and commercially available materials. This simple experimental set-up, drastic reduction in reaction time, one-pot synthesis combined with easy recovery of IL and recyclability, contribute to the development of a green strategy making the technology practical, easy to perform and facile.

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, Kakatiya University Warangal, India for providing the facilities, K. Govardhan Reddy is thankful to UGC, New Delhi, India for the award of a fellowship (JRF).

References

(1) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083
(2) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789.
(3) Wu, H-H.; Yang, F.; Cui, P.; Tang, J.; He, M-Y. *Tetrahedron Lett.* **2004**, *45*, 4963–4965.
(4) Wang, H.; Cui, P.; Zou, G.; Yang, F.; Tang, J. *Tetrehedron* **2006**, *62*, 3985–3988.
(5) Zhu, H.P.; Yang, F.; Tang, J.; He, M-Y. *Green Chem.* **2003**, *5*, 38–39.
(6) Chu, C.D.; Qi, Y.H.; Hao, W. *Catal. Commun.* **2007**, *8*, 1527–1530.
(7) Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* **2004**, *45*, 265–268.

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(8) Chakraborti, A.K.; Raha Roy, S.; Kumar, D.; Chopra, P. *Green Chem.* **2008**, *10*, 1111–1118.
(9) Chakraborti, A.K.; Raha Roy, S. *J. Am. Chem. Soc.* **2009**, *131*, 6902–6903.
(10) Sarkar, A.; Raha Roy, S.; Chakraborti, A.K. *Chem. Commun.* **2011**, *47*, 4538–4540.
(11) Raha Roy, S.; Chakraborti, A.K. *Org. Lett.* **2010**, *12*, 3866–3869.
(12) Reddy, P.S.; Kanjilal, S.; Sunitha, S.; Prasad, R.B.N. *Tetrahedron Lett.* **2007**, *48*, 8807–8810.
(13) Billmann, J.H.; Dorman, L.C. *J. Med. Chem.* **1963**, *6*, 701–708.
(14) Sridhar, D.R.; Reddy Sastry, C.; Lal, B.; Reddy, G.S.; Bhopale, K.K.; Khokar, R.S.; Tripathi, K. *Indian J. Chem.* **1980**, *19B*, 1065–1067.
(15) Hishmat, O.H.; Rahman, A.H.; El-Ebrashi, N.M.A.; Diwani, H.I.; El- Diwani, A.I. *Indian J. Chem.* **1983**, *22B*, 313–315.
(16) Dwivedi, A.K.; Shukla, V.K.; Bhandari, K.; Setty, B.S.; Komboj, V.P.; Khanna, N.H. *Indian J. Chem.* **1991**, *30B*, 281–285.
(17) Mellar, J.H.; Merriman, G.D.; Riviere, P. *Tetrahedron Lett.* **1991**, *32*, 7103–7106.
(18) Ujjinamatada, R.K.; Appala, R.S.; Agasimundin, Y.S. *J. Hetrocyclic Chem.* **2006**, *43*, 437–441.
(19) Bruno, K.; Gabriel, M.; Michael, H.H. *Tetrahedron Lett.* **1984**, *25*, 3837–3840.
(20) Gurupadayya, B.M.; Mayohara, Y.N.; Gopal, M. *Indian J. Heterocyclic Chem.* **2005**, *15*, 113–116.
(21) Rajanarendar, E.; Mohan, G.; Reddy, A.S. *Indian J. Chem.* **2008**, *47B*, 112–116.
(22) Rajanarendar, E.; Raju, S.; Reddy, A.S.; Reddy, K.G.; Reddy, M.N. *Chem. Pharm. Bull.* **2010**, *58*(6), 833–839.
(23) Rajanarendar, E.; Reddy, A.S.; Raju, S.; Firoz, P.S.; Reddy, K.G. *Chinese J. Chem.* **2011**, 29, 769–772.
(24) Rajanarendar, E.; Ramamurthy, K.; Reddy, M.N. *Indian J. Hetrocyclic Chem.* **2010**, *19*, 417–418.
(25) Rajanarendar, E.; Rama Murthy, K.; Firoz, P.S.; Nagi Reddy, M. *Indian J. Chem.* **2011**, *50B*, 587–592.
(26) Rajanarendar, E.; Reddy, M.N.; Firoz, P.S. *Indian J. Chem.* **2011**, *50B* 245–252.
(27) Rajanarendar, E.; Ramesh, P.; Mohan, G.; Rao, E.K. *J. Hetrocyclic Chem.* **2007**, *44*, 483–486.
(28) Rajanarendar, E.; Ramesh, P.; Srinivas, M.; Ramu, K.; Mohan, G. *Synth. Commun.* **2006**, *36*, 665–671.
(29) Rajanarendar, E.; Reddy, M.N.; Ramamurthy, K. *Chinese Chem. Lett.* **2010**, *21*, 927–930.
(30) Rajanarendar, E.; Raju, S.; Reddy, M.N.; Ramamurthy, K.; Rama Krishna, S.; Kiran, L.H.; Reddy, R.N.; Reddy, Y.N. *Eu. J. Med. Chem.* **2012**, *50*, 274–279.
(31) Moreira, D.N.; Zanatta, N.; Bonacorso, H.G. *Chem. Rev.* **2008**, *108*, 2015–2050.
(32) Kitazume, T.; Zulifiqar, F.; Tanaka, G. *Green Chem.* **2000**, *2*, 133–136.
(33) Holberg, J.D.; Seddon, K.R. *J. Chem. Soc. Dalton Trans.* **1999**, *13*, 2133–2140.
(34) Namboodiri, V.; Varma, R.S. *Org. Lett.* **2002**, *4*, 3161–3163.
(35) Ranu, B.C.; Benarjee, S. *Org. Lett.* **2005**, *7*, 3049–3052.

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