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Green synthesis of substituted imidazothiadiazoles using ionic liquid

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An eco-friendly facile synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles is described using ionic liquid, [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate). The use of recyclable catalyst demonstrates the advantages of significant rate enhancement along with improved yields. The protocol is green and effective for producing the desired target moiety.

Keywords: Thiadiazole, ionic liquid, α-bromoacetophenone, imidazo[2,1-*b*]-1,3,4-thiadiazoles, green chemistry

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Green chemistry is placed in the frontier areas of research and has been focussed for considerable recent research. Green chemistry is not a new branch of chemistry, it is rather a thought process on existing and new tools, knowledge and design of chemistry in such a way that it contributes to the societal economy while protecting the environment and human health. Green chemistry[1-3] revolves around the design, development and implementation of chemical processes and products that reduce or eliminate hazardous substances in a way that is feasible and economically viable. It encompasses a variety of disciplines: prevention of waste formation, products formed should be biodegradable, preferred use of catalysts, development of low cost route, use of auxiliary substances, designing safer chemicals and optimum utilisation of energy. Various green strategies have been worked out. The reduction or the replacement of volatile organic solvents from the reaction medium is of utmost importance with possible substitutions by non-volatile or recyclable alternatives. In recent years, room temperature ionic liquids (RTILs)[4-6] are attracting increasing interest as green recyclable alternative to classical molecular solvents for synthetic organic chemistry.

Ionic liquids are basically liquids at room temperature. They are composed entirely of ions and can be represented as $[cation]^+[anion]^-$. Various cations can be tetraalkylammonium, tetralkylphosphonium, trialkylsulfonium, *N*-alkylpyridinium, 1,3-dialkylimidazolium cations. Their respective structures are shown in **Figure 1**.

Various anions can be NO_3^-, Cl^-, Br^-, I^-, $AlCl_4^-$, BF_4^-, PF_6^-, CH_3COO^-, F_3CCOO^-, $CF_3SO_3^-$ and $(CF_3SO_3)_2N^-$.

The present paper illustrates the versatility of the ionic liquid [bmim][PF_6], 1-butyl-3-methylimidazolium hexafluorophosphate (**Structure 1**).

Till date, many of the important reactions have been investigated in this particular ionic liquid. Their application includes the synthesis of 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones[7], *N*-alkyl/arylimides[8], pravadoline[9], *etc*.

The ionic liquid, [bmim][PF_6] is utilised for synthesizing 2,6-disubstituted imidazo[2,1-*b*]-1,3,4-thiadiazoles by the condensation of α-bromoacetophenone derivative with 5-alkyl-2-amino-1,3,4-thiadiazoles[10]. As a test case to standardize the reaction, the reaction was investigated under different reaction conditions. The reaction was performed in conventional organic solvents, ethanol and *N,N*-dimethylformamide (**Table I**). This gave poor yields and reaction took several hours to complete. Then the same reaction was attempted in ionic liquid [bmim][PF_6] in presence catalytic amount of base which to our surprise gave excellent yields within an hour of reaction. Then the reaction with the same ionic liquid was tried using different bases, triethylamine and sodium carbonate (**Table I**). Best result in terms of yield as well as reaction time was obtained with the use of sodium carbonate. So the use of sodium carbonate is preferred as it is a mild water soluble inorganic base which catalysed the reaction

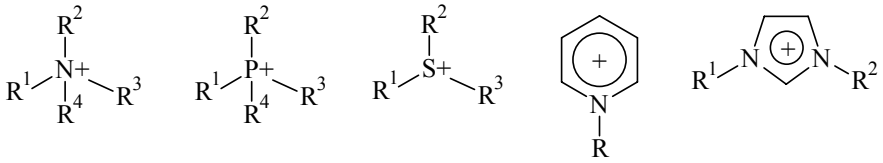
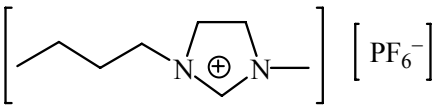


Figure 1



Structure 1 — Ionic liquid [bmim]PF_6

Table I — Cyclocondensation of α-bromoacetophenone **1a** with 5-phenyl-2-amino-1,3,4-thiadiazole **2a** in different solvents to form **3a**

Entry	Solvent	Reaction temperature (°C)	Reaction time (hr)	Yield (%)
1	EtOH	80	4	62
2	DMF	80	3	60
3	[bmim]PF_6[a]	60	1	78
4	[bmim]PF_6[b]	60	1	80

[a] NEt_3 was used as the base and the amount of [bmim]PF_6 used was 2 mL.
[b] Na_2CO_3 was used as the base and the amount of [bmim]PF_6 used was 2 mL.

and whatever is left unused can easily be removed by aqueous work-up giving rise to the green route to imidazothiadiazoles.

In a similar fashion, the reaction is found to be generally applicable with variations in both the reacting components. The products are obtained in quantitative yields (**Table II**, **Scheme I**). The products **3a-h** are characterized by ^{1}H NMR, IR and melting points which are in accordance with the literature data. Thus, the ionic liquid plays the dual role of solvent as well as promoter.

The ionic liquid can be typically recovered by extracting out the product first and filtering the suspension to remove residual solid followed by vacuum drying. The recovered solvent can be reused with no appreciable decrease in yield. The representative result is summarized in **Table III**.

In conclusion, the reactions in ionic liquids give a flavour of what can be achieved in these neoteric solvents. Because the properties of the ionic liquid can be adjusted to suit an individual reaction type, they can truly be described as designer solvents. We have shown that by choosing the correct ionic liquid,

Table II — Reaction of α-bromoacetophenone and its *p*-chloro derivative **1a-b** with 5-alkyl/aryl-2-amino-1,3,4-thiadiazoles **2a-f**

Entry	R	R'	Method A[a]		Method B[b]	
			Time (hr)	Yield (%)	Time (min)	Yield (%)
1	C_6H_5	H	4	62	60	80
2	H	H	3	65	45	82
3	CH_3	H	4	62	60	80
4	*n*-C_7H_{15}	H	5	60	70	77
5	*n*-C_6H_{13}	H	5	60	70	80
6	4-CH_3O-C_6H_4	H	3	62	50	80
7	*n*-C_7H_{15}	4-Cl	5	62	80	78
8	*n*-C_6H_{13}	4-Cl	5	62	80	78

[a] Reaction temperature is 80°C
[b] Reaction temperature is 60°C

Table III — Recycling of [bmim]PF_6 (2 mL) for the synthesis of **3a**

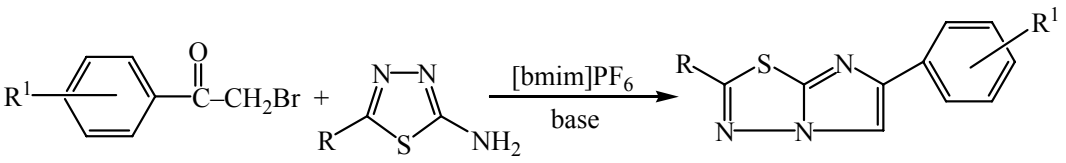
Entry	Cycle	**3a** Yield[c] (%)
1	1	80
2	3	78

[c]Entry **4** in **Table I**.

high product yields can be obtained and a reduced amount of waste can be produced in a given reaction with the elimination of solvents. The reactions are quicker, facile and much more convenient to carry out as compared to conventional organic solvents, thus contributing to green chemistry.

Experimental Section

Melting points were taken in a Thomas Hoover melting point apparatus and were corrected. IR (KBr) spectra were obtained on a Perkin-Elmer FTIR 1710 spectrophotometer. ^{1}H NMR were recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as an internal standard (chemical shifts, in δ). The compounds purity was checked on silica gel coated aluminium plates (Merck). Temperature of the reaction mixture was noted with mini gun type IR thermometer. The ionic liquid [bmim]PF_6 was



1a-b **2a-f** **3a-h**

1a R^1 = H
1b R^1 = 4-Cl

2a R = Ph
2b R = H
2c R = CH_3
2d R = *n*-C_7H_{15}
2e R = *n*-C_6H_{13}
2f R = 4-CH_3O-C_6H_4

3a R^1 = H, R = Ph
3b R^1 = H, R = H
3c R^1 = H, R = CH_3
3d R^1 = H, R = *n*-C_7H_{15}
3e R^1 = H, R = *n*-C_6H_{13}
3f R^1 = H, R = 4-CH_3O-C_6H_4
3g R^1 = 4-Cl, R = *n*-C_7H_{15}
3h R^1 = 4-Cl, R = *n*-C_6H_{13}

Scheme I

synthesized according to the reported procedure[11]. Also, 5-alkyl/aryl-2-amino-1,3,4-thiadiazoles **2a-f** were prepared according to the literature method[12,13].

General procedure for the synthesis of 2,6-di-substituted-imidazo[2,1-*b*]-1,3,4-thiadiazoles, 3a-h

Method A: Conventional organic solvent mediated synthesis of 3a-h

A mixture of α-bromoacetophenone or its *p*-chloro derivative (**1a-b**, 0.01 mole) and 5-alkyl/aryl-2-amino-1,3,4-thiadiazole (**2a-f**, 0.01 mole) in ethanol (20 mL) was refluxed for the appropriate time. The progress of reaction was monitored by TLC and upon completion, the reaction mixture was cooled and neutralized with ammonical solution at 10°C. The resulting solid was filtered, washed with water and purified by recrystallization from aqueous ethanol.

Method B : Ionic liquid mediated synthesis of 3a-h

A mixture of α-bromoacetophenone and its *p*-chloro derivative (**1a-b**, 0.01 mole), 5-alkyl/aryl-1,3,4-thiadiazole (**2a-f**, 0.01 mole) and sodium carbonate (0.005 mole) in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]PF_6 (2 mL) was stirred at 60°C for the appropriate time (**Table I**). After completion of reaction, as determined by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined ethereal extracts were concentrated *in vacuo* and the resulting product was purified by preparative TLC (benzene:ethyl acetate v/v 7:3) to afford imidazo[2,1-*b*]-1,3,4-thiadiazoles, **3a-h**. After isolation of the product, the remainder of the ionic liquid was further washed with diethyl ether, filtering the suspension to remove residual sodium carbonate and precipitated sodium bromide, followed by drying under vacuum and reused in the next turn (**Table III**).

The spectroscopic data obtained for **3a-h** were in agreement with the literature values.

2,6-Diphenylimidazo[2,1-*b*]-1,3,4-thiadiazole, **3a**: m.p. 206-08°C (lit.[14] m.p. 206°C).

6-Phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 3b: m.p. 130-32°C (lit.[15] m.p. 132°C).

2-Methyl-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 3c: m.p. 135-37°C (lit.[15] m.p. 137°C).

2-Heptyl-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 3d: m.p. 216-18°C (lit.[16] m.p. 220°C).

2-Hexyl-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 3e: m.p. 100-02°C (lit.[16] m.p. 100°C).

2-(4-Methoxyphenyl)-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 3f: m.p. 220-22°C (lit.[14] m.p. 227°C).

2-Heptyl-6-(4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole, 3g: m.p. 106-08°C (lit.[16] m.p. 104°C).

2-Hexyl-6-(4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole, 3h: m.p. 109-11°C (lit.[16] m.p. 112°C).

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