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Ionic Liquid (I_2 [bmim]BF_4) : A highly efficient green catalytic system for synthesis of 2-amino, 5-aryl, 1, 3, 4-thiadiazoles

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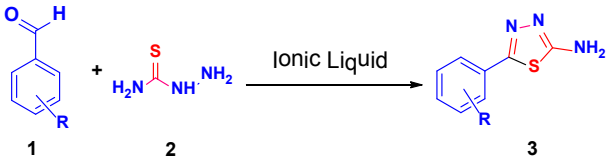
Abstract: Present research work is a simple and an efficient method for the synthesis series of 2-amino Thiadiazole (**3a-j**) starting from aromatic aldehydes (**1a-j**) and thiosemicarbazide (**2**) in the presence of a catalytic amount of [bmim]BF_4 ionic liquid as economical and non-toxic molecular iodine under mild conditions at room temperature and below some arbitrary temperature at 100°C. Molecular iodine acts faster in ionic liquids when compared to conventional solvents such as DMSO, DMF, THF and acetonitrile. The reaction carried out at room temperature with good to excellent yields and the final compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR analysis.

Keywords: Ionic Liquid, Molecular Iodine, 2-amino, 5-aryl,1,3,4-thiadiazoles, Conventional method.

Introduction

An environmentally benign solvents as Ionic liquids (ILs) have been recently gained appreciation in various chemical processes because of their many interesting and fascinating properties [1-6]. The room temperature ionic liquids (RTILs) as imidazolium are very interesting solvent media which can act as 'organized solvents'[6]. The properties act as 'entropic drivers'[7], co-solvents[8]. It can be recovered and re-used for a number of runs with negligible loss of its activity[8]. The use of Molecular Iodine (MI) in organic synthesis has been known for a long time, such as in the Grignard Reaction (GR) [9]. MI has received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations under very mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity [10].

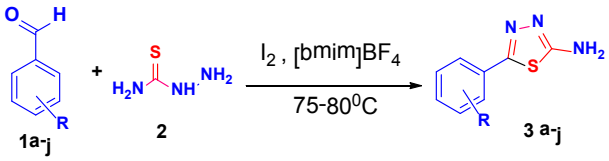


Scheme 1. Synthesis of 2-amino 1,3,4 Thiadiazole derivatives catalyzed by ionic liquid.

Previously used MI and or Ionic liquid; Depyranylation in methanol for few hours [11]. Similarly, selective protection of one hydroxyl group as its tetrahydropyranyl ether in symmetrical diols is achieved by iodine-catalyzed reaction [12-13]. A mild and rapid trimethylsilylation of a wide variety of alcohols using hexamethyldisilazane (HMDS) and a catalytic amount of iodine [14]. Iodine was also shown to catalyze the procedure for the immediate conversion of various organo-phosphonates under neutral conditions using HMDS [15]. The thioketalization for various carbonyl compounds in high yields [16]. Solvent free condition in catalytic amount of iodine supported on a neutral alumina surface [17]. Aldehyde, anhydride to acetate [18], O-glycosidation and C-glycosidation of allyltrimethylsilane [19-20]. The elemental iodine has been utilized in cycloaddition reaction, trans-annelated pyrano [3,2-c]benzopyrans in high yields and with high diastereoselectivity [21]. In highly rapid synthesis of bis(indolyl) methanes under mild conditions [22-23] and simple synthesis of substituted pyrroles using modified Paal–Knorr methods [24].

Nitrogen and Sulfur containing five member heterocycles such as azoles, thiazole, diazole in particular that 2-amino Thiadiazole scaffold are well-known biologically active compounds as anti-parasitic, anti-convulsan and anti-coagulant [25], anti-microbial [26], anti-cancer [27], anti-inflammatory [28-29] anti-tubercular [30],anti-fungal [31], diuretic [32], anthelmintic activity [33], anti-tumor [34], anti-diabetic [35], anti-platelet [36].

In the recent past, synthesis of amino thiadiazole and its derivatives [37].In earlier our research work to develop research methodology for the synthesis of 2-amino, 5-aryl 1,3,4-Thiadiazoles [38], In continuation of our green approach research work [39],herein we report synthesis of 2-amino, 5-aryl 1,3,4-Thiadiazoles using molecular iodine and ionic liquid catalyst and solvent over those hazardous acid catalyst such as $POCl_3$, $SOCl_2$, Conc.H_2SO_4, acid-anhydride etc.



Scheme 2. Synthesis of 2-amino 1, 3, 4-thiadiazole derivatives in Molecular Iodine (MI) and Ionic liquid.

Results and discussion

In order to elucidate the role of catalyst, a control reaction was carried out using equimolar reactants; benzaldehyde (10mmole) and thiosemicarbazide (10 mmol) in the absence of any catalyst under solvent free condition. TLC indicated no product formation even after 8 h at 70°C-80°C (Table1, entry no 1). However, when the same reaction was carried out in the presence of catalytic amount of molecular iodine (1-2mmole), THF, DMSO, DMF, Acetonitrile, [bmim]BF_4 , Ethanol there is no significant effect was observed at room temperature condition whereas increasing temperature room temperature to 60°C, 70°C and 80°C in ionic liquid [bmim]BF_4 the product could be Isolated in not only quantitative but also qualitative yields within 3 hours at 75-80°C under atmospheric pressure (Table 1 entry 7,8) in higher yield 99% (Scheme 1, R=H).

Herein molecular iodine plays an important role in reaction media by polarizing the carbonyl group of the substrate, thereby enhancing the electrophilicity of the carbonyl carbon. This facilitates the nucleophilic reaction of the amino and thio group of the Thiosemicarbazide. Thus we decided that all examples were tested in ionic liquid [bmim]BF_4 in catalytic amount of molecular iodine with excellent yield = 91-99% at 75-80°C (Table 2). The ionic liquid were re-used for four to five cycles, the better yield was obtained for first four cycle of the reaction (Figure 1), further cycles of reaction yield of the product were decreases even after increasing the time as well as temperature. An electronic effect was observed, electron withdrawing groups (-NO_2) gave better yield than electron donating groups to aromatic aldehyde, five member heterocycles such as thiophene carbaldehyde and furfural / furan carbaldehyde gave corresponding yield (Table 2).Finally, the structure of compounds were substantiated by IR and ^{1}H NMR and ^{13}CNMR spectra and compared with their reported methods [37].

3.1 Recycle of Ionic Liquid:

Recyclability: Efficient recyclability of ionic liquid reaction media could be achieved with each successive run. The relation between the number of cycles of the reaction and the

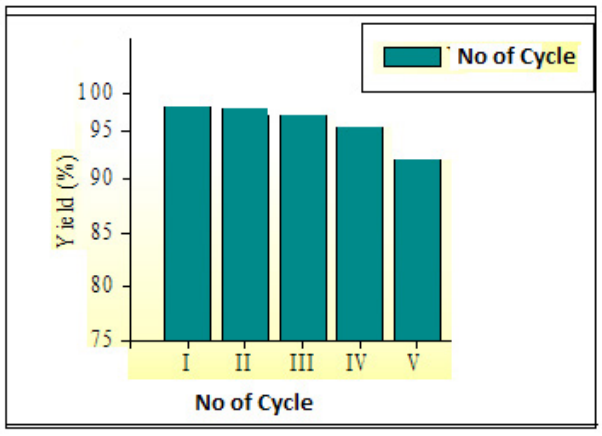


Figure 1: **Recycle of Ionic Liquid:** Optimisation for the Synthesis of 2-amino, 1,3,4 Thiadiazoles: Solvent effect.[a]Reaction conditions: thiosemicarbazide (10 mmol), aromatic aldehyde (10 mmole), molecular iodine (1mmole) and ionic liquid [bmim]BF_4 (5ml) at room temperature under atmospheric pressure. Isolated pure crystallized product.

The advantage of using ionic liquid is that the products of the reaction can be extracted into the organic solvent (ethyl acetate) leaving the ionic liquid behind which can be successfully recycled.

Table 1.Screening of solvents with temperature for 2-amino, 5-aryl, 1, 3, 4-thiadiazoles by conventional method:

Entry	Solvent	Temperature (°C)			Yield[a] (%)/ Time(h)		
		I	II	III	I	II	III
1	Without	40	60	75	00/4	00/6	00/8
2	THF	40	60	75	00/3	60/3	86/3
3	DMF	40	60	75	00/3	50/3	58/3
4	Acetonitrile	40	60	75	00/3	60/3	83/3
5	DMSO	40	60	75	00/3	58/3	70/3
6	Ethanol/ Reflux	40	60	75	00/3	62/3	90/3
7	**[bmim]BF_4**	40	60	75	00/3	70/3	**99/3**
8	[bmim]BF_4	40	60	80	00/3	70/3	99/3

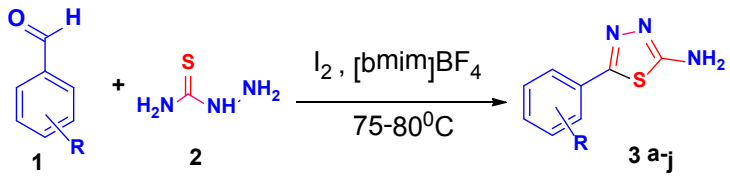
[a]***Reaction Condition [Conventional method]:*** Benzaldehyde (10 mmole), thiosemicarbazide (10 mmol), and catalytic amount of iodine (1mmole) in solvent (5ml) were stirred for 3 h at room temperature and below some arbitrary temperature at 100°C., [a] Isolated yield.

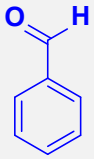
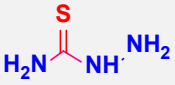
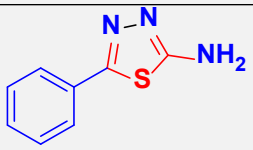
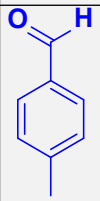
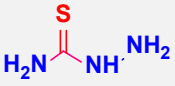
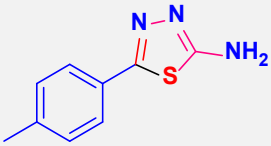
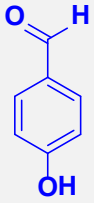
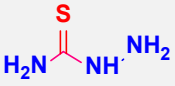
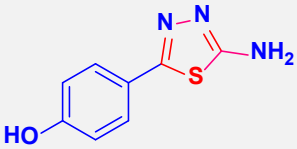
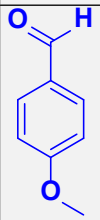
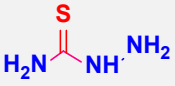
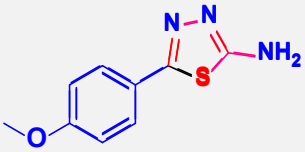
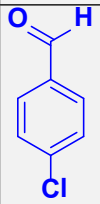
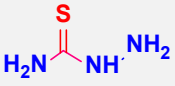
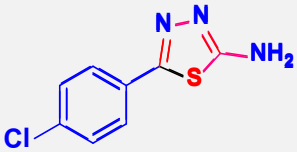
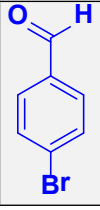
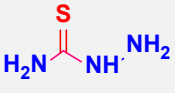
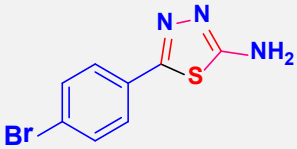
The advantage of using ionic liquid is that the products of the reaction can be extracted into the organic solvent (ethyl acetate) leaving the ionic liquid behind which can be successfully recycled.

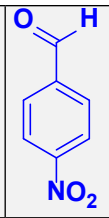
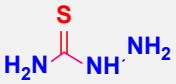
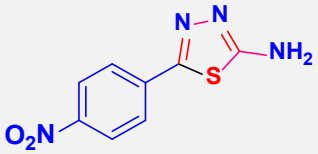
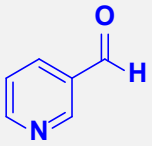
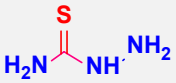
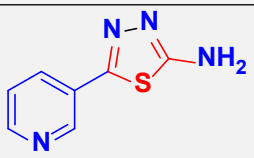
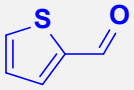
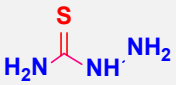
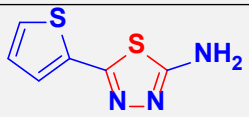
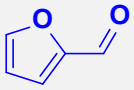
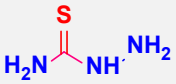
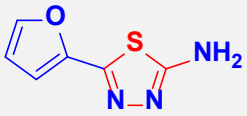
Experimental

General

Table 2.Synthesis of 2-amino 1, 3, 4-thiadiazole derivatives in Molecular iodine and Ionic liquid[a].



Entry	Structure of reactant (1)	Structure of reactant (2)	Structure of product (3)	Yield[b] (%)/ Time (h)	Melting Point (^{0}C)
1			 3a	99/3	224-225
2			 3b	92/3	219-220
3			 3c	91/3	138-139
4			 3d	93/3	192-193
5			 3e	95/3	229-230
6			 3f	92/3	228-230

7			 3g	99/3	258-259
8			 3h	96/3	240-241
9			 3i	91/3	256-257
10			 3j	91/3	248-250

[a]***Reaction Condition:*** aromatic aldehyde (10 mmole), thiosemicarbazide (10 mmol), and catalytic amount of iodine (1mmole)in ionic liquid, 1-butyl-3-methylimidazolium tetra fluoroborate (5ml) were stirred for 3 h. [b]Isolated yield.

Starting materials were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected. IR spectra were run for KBr disc on Perkin-Elmer 120-000 A. apparatus (υ_{max} in cm^{-1}), ^1H spectra were recorded on a Bruker spectrometer 300 MHz, $DMSOd_6$ as a solvent. Chemical shifts are reported as δ_{ppm} units.

Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine (3a-3j):

Benzaldehyde/Substituted aryl/heterocyclic aldehyde (10 mmole) **1**, thiosemicarbazide (10 mmol)**2**, and catalytic amount of iodine (1mmole) dissolve in 5ml of 1-butyl-3-methylimidazolium tetra fluoroborate and were stirred for appropriate time Table **1**. Progress the reaction on TLC, after completion of reaction the solvent was evaporated under vacuum and basify with 10% Na_2CO_3. Crystallization by ethanol gave product (91- 99 %)Table **2**.

Spectral Characterization data:

5-phenyl-1,3,4-thiadiazol-2-amine (3a):

IR (cm^{-1}): 3406, 3150, 1050, 680.; ^{1}HNMR: δppm = 6.96 (s, 2H, $-NH_2$), 7.40-8.06 (m, 5H, Ar-H).

^{13}C NMR: δ ppm= 174.2, 161.2, 133.2, 130.4, 129.4, 128.2.

5-(p-tolyl)-1,3,4-thiadiazol-2-amine (3b):

IR (cm^{-1}): 3215, 3152, 1505, 1180, 1050, 690.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 2.32 (s, 3H, $-CH_3$), 7.28 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm=174.2, 161.3, 131.2, 130.5, 129.3, 127.6, 21.3.

4-(5-amino-1,3,4-thiadiazol-2-yl)phenol (3c):
IR (cm^{-1}): 3390, 3150, 3140, 1480, 1450, 1050,715.; ^{1}H NMR : δ ppm =6.96 (s, 2H, $-NH_2$), 5.30 (s, 1H, -OH), 6.83 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.3, 158.2, 128.9, 126.2, 116.2.

5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine (3d):

IR (cm^{-1}):3415, 3150, 1530, 1402, 1050.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 3.82 (s, 3H), 7.01 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm=174.2, 161.2, 160.0, 128.7, 125.2, 114.8, 55.2.

5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (3e):

IR (cm^{-1}):3340, 3153, 1520, 1050, 670.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 7.52 (d, 2H, Ar-H), 8.02 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.7, 134.2, 131.2, 129.3, 128.2.

5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine(3f):

IR (cm^{-1}):3350, 3150, 1531, 1052, 680.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 7.82 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.3, 132.6, 132.2, 129.2, 123.2.

5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine(3g):

IR (cm^{-1}):3410, 3150, 1512, 1022, 620.; ^{1}H NMR: δ ppm =6.96 (s, 2H,$-NH_2$), 8.68 (d, 2H, Ar-H), 8.29 (d, 2H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.2, 147.8, 139.9, 128.6, 124.2.

5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (3h):

IR (cm^{-1}):3455, 3405, 3150, 1515,1060, 675.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 9.20 (s, 1H, Ar-H), 8.40 (d, 1H, Ar-H), 8.70 (d, 1H, Ar-H), 7.53 (t, 1H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.2, 148.3, 147.2, 134.1, 133.2, 124.2.

5-(thiophen-2-yl)-1,3,4-thiadiazol-2-amine (3i):

IR (cm^{-1}): 3412, 3150, 1516, 1345, 1060, 675.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 7.82 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.16 (t, 1H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.5, 128.6, 128.4, 128.1, 127.5.

5-(furan-2-yl)-1,3,4-thiadiazol-2-amine (3j):

IR (cm^{-1}): 3406, 3160, 1520, 1065, 689.; ^{1}H NMR: δ ppm =6.96 (s, 2H, $-NH_2$), 7.82 (d, 1H, Ar-H, 7.06 (d, 1H, Ar-H), 6.65 (t, 1H, Ar-H).; ^{13}C NMR: δ ppm= 174.2, 161.6, 146.3, 146.1, 112.3, 112.0.

Conclusion:

As part of an ongoing interest in exploring various green methods for organic transformations, we developed reported 2-amino, 5-aryl, 1, 3, 4-thiadiazoles using molecular iodine catalyst at room temperature and below some arbitrary temperature at 100°C. in ionic liquid as an inexpensive, versatile, non-toxic and a readily available catalytic procedure that can serve as a green alternative method for this important of reaction. For the first time, the use of iodine in ionic liquids (as a novel and recyclable polar reaction media) is being reported for the synthesis of 2-amino, 1, 3, 4-thiadiazoles derivatives using aryl aldehydes and thiosemicarbazide as commercially available starting materials**.**

Conflict of interest:

The authors confirm that this article content has no conflict of interest.

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