SONOCHEMICAL SYNTHESIS OF 2-IMINO-IMIDAZOLES USING 1-BUTYL-3-METHYL IMIDAZOLIUM TETRAFLUROBORATE

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ABSTRACT
A rapid sonochemical synthesis of 2-imino imidazoles using solvent and catalyst 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF₄]. The overall merits of this reaction are faster rates, milder conditions, higher yields, shorter time and facile workup. The simplicity of the reaction facilitates the delineation of a green chemistry methodology: use of designer solvent as catalyst and ultrasound irradiation, to define useful protocol for optimal conversions.

Keyword: Ultrasonic irradiation, [BMIM][BF₄] ionic liquid, 2-imino imidazole.

1. INTRODUCTION
Ultrasound irradiation offers an unconventional energy source for organic reactions which are consistently accomplished by heating. This technology has progressively refined for definition of simple, clean and convenient chemical transformations [1-3]. Organic reactions are accelerated, the number of steps involved is reduced, and cruder reagents can be used under sonic conditions. Sonication initiates several extreme conditions inside and around the reaction mixtures. Cavitation induces increase in the rates and selectivity of most chemical reactions, formation and growth of vapour/gas bubbles in a liquid, which oscillate, pulsate and coalesce. These effects of ultrasound are achieved due to the phenomenon of acoustic cavitations [4] and the primary chemical reactions are due to the transient state of high temperatures and pressures [5].
There are two basic approaches to the explanation of high-energy effects caused by cavitation: thermal and electrical ones. In the thermal approach, these effects are associated with high temperature inside a cavitation bubble based upon its adiabatic compression at a continuously increasing rate; in the electrical approach these are related to a discharge inside the bubble resulting from the accumulation of electric charges on its walls. These bubbles can undergo a violent collapse. Upon cavity collapse, molecules present inside or around the cavity can dissociate and form radicals. The cavitation dynamics and corresponding temperature rise are strongly determined by the physicochemical properties of the liquid and gases dissolved [6]. Examples of liquid properties include bulk temperature, viscosity, and surface tension. In addition, the characteristics of the imposed sound field, i.e. intensity and frequency are also of considerable importance. For instance, a higher ultrasound frequency enhances the number of collapses per unit time, whereas the intensity of cavitation collapse decreases [7].

Extensive research on synthetic methodologies for imidazoles has been reported. Tetra substituted imidazoles is a core nucleus in many therapeutically relevant moieties such as Losartan, and Olmesartan. Imidazole and their derivatives usually possess diverse biological activities and play important roles as versatile building blocks for the synthesis of natural products and therapeutic agents [8, 9]. Many of the substituted imidazoles and 2-amino imidazoles have fungicidal [10], herbicidal [11], antiasthmatic [12], anti-inflammatory [13], antiulcerative [14] and antithrombotic [15] activities. These types of compounds also function as plant growth regulators and therapeutic agents [16]. Imidazoles have been reported to serve as anti-HIV, anti-convulsant [17], antisenescence [18], anti-muscarinic [19], antiarthritic [20], cardiotonic [21], non sedative anxiolytic [22], inhibitors of Acyl CoA Cholesterol O-acyl transferase (ACAT) [23], HMG CoA reductase (HMGR) [24], calcium antagonist and inhibitors of thromboxane A2 synthase [25], antihistaminic [26], tranquillizers [27], anti-Parkinson [28] and MAO inhibitors [29].

There are many available classical routes for the synthesis of imidazoles, in particular 4, 5 disubstituted 2-aminoimidazoles [30-34] condensation of α-aminocarbonyl compound with cyanoamide or isothiourea [33], cyclocondensation of aldehydes and guanidine nitrate using sodium cyanide supported aluminum oxide and reaction of α-haloketones with N-acetylguanidine. [31] However, some of these methods are pH sensitive and can result in the self-condensation, ring cleavage, [35] use of expensive starting materials, harsh reaction
conditions, numerous steps and unit operations, long reaction times, and low yields. Recently, some modifications have been carried out in the presence of protic or Lewis acids such as H₃PO₄ [36], silica sulfuric acid [37], I₂ [38], NiCl₄.H₂O [39], H₄ [PMo₁₁VO₄₀] [40], [Hbim]BF₄ [41] or [HeMIM]BF₄ [42] under reflux condition or microwave irradiation. Khosropour [43] described the synthesis of 2, 4, 5 trisubstituted imidazole catalyzed by Zr (acac) under ultrasound at ambient temperature.

A selective oxidation of alcohols into aldehydes and ketones under sonication by metal nitrates i.e. Ni (NO₃)₂.6H₂O/I₂/water, FeCl₃/HNO₃ system has been reported [44, 45]. Despite intensive efforts, few general methods exist for the construction of imidazole scaffolds [46-53]. An efficient approach that is viable for designed library synthesis will be desirable.

The ionic liquid [BMIM][BF₄] (1-butyl-3-methylimidazolium tetrafluoroborate), a ‘designer solvent’ has proved to be as a ‘neoteric solvent’ for various chemical reactions. The advantages include non-volatility, low melting point, low viscosity as well as thermal and electrochemical stability [54]. Recently, we have reported a convenient synthesis of a library of pyrimidine-isoxazoline hybrids in [BMIM][PF₆] –water/KOH at ambient temperature [55]. Our success in exploiting the versatility and environmentally benign nature of ionic liquids encouraged us to extrapolate these results to the synthesis of imidazoles in ionic liquid under ultrasound irradiation.

[BMIM][BF₄], hydrophilic ionic liquid is well known for its various catalytic applications. Particularly, hydrophilic media possessing tetra fluoroborate [BF₄] anions have a multitude of usages in different biochemical and chemical reactions [56]. We illustrate herein, its expanding use in reactions on diversely substituted substrates.

Acetonitrile (ACN) is suggested to be a co-solvent of room-temperature ionic liquids (RTILs) in order to decrease their unprecedented viscosity and increase ionic transport. RTILs are usually positioned as nontoxic, green solvents, mainly due to their negligible volatility. Chaban and Prezhdo [57] et al investigated the volatility of the imidazolium-based RTILs/ACN mixtures on the basis of the atomistic precision simulations of liquid/vapour interfaces over a wide composition range and observed noticeable decrease in the volatility.

We embarked on the synthesis of 2-imino imidazoles accommodating imidazole and phenols within a same molecular framework using RTILs, [BMIM][BF₄]/ACN mixtures. We explored a pathway of synthesis of biologically active imidazole moieties under ultrasound
irradiations at various frequencies for time ranging from 30 to 120 mins in [BMIM][BF₄]. The reaction rate was sluggish in organic solvents.

2. EXPERIMENTAL

2.1. Chemicals and apparatus

Chemical reagents like acetonitrile, ethylene glycol, DMF, piperidine, pyridine in high purity of AR grade were purchased from Merck Chemical Company. Guanidine carbonate was procured from Lancaster Germany. [BMIM][BF₄] was acquired from Aldrich (USA) Ltd and was used without further purification. The solvents were purified before prior use wherever required by standard methods.

Melting points were determined by open capillary method and are uncorrected. All solvents were distilled and dried prior to use. TLC was performed on silica gel G. ¹H NMR and ¹³C NMR spectra were recorded in DMSO-d₆ and CDCl₃ solutions respectively on a Brucker AC 400 (MHz) instrument. Chemical shifts are reported in ppm using TMS as an internal standard. IR spectra were obtained on a Perkin Elmer 1800 spectrophotometer using KBr discs and Mass spectra were measured with Shimadzu gas chromatograph coupled with QP5050 Spectrometer at 1-1.5 eV. The reactions were carried out with a high temp Ultrasonic Cleaner (Sm 200 US), (with a temp range upto 80°C for continuous process), tank size: 14”x12”x8”(H), 20 Litres, 35 kHz, power 400 watts.

2.2. General procedure for synthesis of 2-(imino-4, 5-dihydro-dihydro-1H-imidazol-4-yl)-substituted phenols under thermal condition (3a-p)

2.2.1. Thermal reaction in organic solvents: Compounds 1a-p was synthesized by a reported procedure. Compound 2 was obtained from Aldrich (USA) and was used without further purification.

A mixture of substituted hydroxyl acetophenones 1, (0.1 mmol) guanidine carbonate 2 (0.2mmol) and molecular Br₂ (0.1 mmol) in acetonitrile (10mL) was refluxed for 16 hrs. The reaction mixture was cooled to room temperature; the solid was poured in ice cold water and filtered. The crude product was purified by crystallization from ethanol to furnish compound 3. The purity of the synthesized material was evaluated by TLC using hexane: ethyl acetate (7:3) as eluent solvent. The reactions were carried out in various organic solvents like ethylene glycol, DMF/ piperidine/pyridine for 8hrs, EtOH/ I₂/NaOH for 12hrs.
2.2.2. Thermal reaction in Room Temperature Ionic Liquids (RTIL): A mixture of substituted hydroxyl acetophenones 1 (0.1 mmol), guanidine carbonate 2 (0.2 mmol) and molecular Br2 (0.1 mmol) in RTIL/Organic solvent (2:1 mL) was refluxed for 6 hrs. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with isopropyl acetate (3x10 mL). The combined isopropyl acetate extracts were concentrated in vacuo; the resulting product was directly charged on to a small silica gel column and eluted with a mixture of hexane: ethyl acetate (7:3) to afford pure 2-(2-imino-1H-imidazol-4-yl)-substituted phenols. The rest of the viscous ionic liquid was further washed with isopropyl acetate and dried at 80°C under reduced pressure to retain its activity in subsequent runs.

2.2.3. Sonochemical reaction in organic solvents and Room Temperature Ionic Liquids (RTIL): An amount of substituted hydroxyl acetophenones 1, (0.01 M), guanidine carbonate 2 (0.02 M) and molecular Br2 (0.01M) dissolved in 1 mL of acetonitrile. The reaction mixture was warmed at 40°C to dissolve the contents. The obtained solution was added drop wise to a thermostated mixture of 2 mL of [BMIM][BF4]. The temperature was kept at 80°C for [BMIM][BF4]/ ACN solvent system. The possibility of adjusting solubility properties by [BMIM][BF4] combinations allows a systematic optimization of the productivity and potential utility of [BMIM][BF4]/ ACN. The reactions were repeatedly carried out in various organic solvents like ethylene glycol, DMF/piperidine/pyridine, EtOH/I2/NaOH, ACN and [BMIM][BF4]/ ACN. In all cases the reaction mixture was irradiated in the water bath of the ultrasonic cleaner at optimized temperature and for the time indicated in Table 1, Table 2 and Table 3. The composition of the reaction mixture was examined, at pre-determined time intervals by TLC. In some cases, the reaction was quenched at a suitable time to avoid the formation of by-products. Then, the reaction mixture was extracted several times with diethyl ether. The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on to a small silica gel column and eluted with a mixture of hexane: ethyl acetate (7:3) to afford pure 2-(2-imino-4,5-dihydro-1H-imidazol-4-yl)-substituted phenols. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs. The pure imidazoles obtained were characterized by IR, 1H NMR, C13 NMR, mass spectra and CHN analysis (Scheme 1).
Scheme 1: Synthesis of 2-(2-imino-4, 5-dihydro-1H-imidazol-4-yl)-substituted phenols under ultrasound irradiation

2.2.4. Recycling of ionic liquid
In the case of the hydrophilic ionic liquid, i.e. [BMIM][BF₄], the reaction mixture was diluted water and extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with water, dried over anhydrous Na₂SO₄ and concentrated in vacuo and the resulting product was purified either by column chromatography or by recrystallization to afford pure product. The ionic liquid can be recovered either by extracting the aqueous phase with ethyl acetate or by evaporating the aqueous layer in vacuo. The ionic liquid thus obtained was further dried at 80°C under reduced pressure for use in subsequent runs.

2.3 Spectral data of synthesized imidazole (3a-p)

2.3.1. 2-bromo-4-6-(2, 5-dihydro-2-imino-1H-imidazol-4-yl) phenol (3a)
White solid, m.p.: 290°C; Yield: 89%; IR (KBr, \( \lambda_{\text{max}}/\text{cm}^{-1} \)): 3541 (OH), 2870 (\(-\text{NH}\)), 1509 (C=N); \(^1\)H NMR (400MHz, DMSO-d₆) \( \delta \): 1.25 (s, 1H, NH), 1.65 (s, 2H, -CH₂), 6.98 (s, 1H, NH), 7.19-7.17 (s, 2H, Ar-H), 10.83 (s, 1H, OH); \(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \) 68.5, 115.7, 124.6, 127.2, 129.6, 131.0, 159.3, 163.2, 164.6; MS: m/z = 288 (M⁺); Anal. Calcd for C₉H₇BrClN₃O: C, 37.46; H, 2.65; N, 15.19. Found: C, 37.24; H, 2.47; N, 14.05 %.

2.3.2. 4-chloro-2-(2, 5-dihydro2-imimo2-amino-1H-imidazol-4-yl)-6-nitrophenol (3b)
White solid, m.p.: 225°C; Yield: 85%; IR (KBr, \( \lambda_{\text{max}}/\text{cm}^{-1} \)): 3385 (OH), 3105 (\(-\text{NH}\)), 1523 (C=N); \(^1\)H NMR (400MHz, DMSO-d₆) \( \delta \): 1.31 (s, 1H, NH); 1.45 (s, 2H, -CH₂), 6.91 (s, 1H, NH), 7.96 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 10.73 (s, 1H, OH); \(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \) 52.6, 109.0, 122.6, 125.4, 128.3, 134.0, 137.5, 163.2, 164.2; MS: m/z = 254 (M⁺); Anal. Calcd for C₉H₇ClN₄O₃: C, 42.45; H, 2.77; N, 22.19. Found: C, 42.24; H, 2.65; N, 22.02 %.
2.3.3. 4-chloro-2-(2, 5-dihydro-2-imino-1H-imidazol-4-yl)-6-iodophenol (3c)
White solid, m.p.: 276°C; Yield: 82%; IR (KBr $\lambda_{\text{max}}$/cm$^{-1}$): 3380 (OH), 3099 (-NH), 1521 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$: 1.34 (s, 1H,NH ); 1.54 (s, 2H, -CH$_2$), 6.21 (s, 1H, N-H), 7.14 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 10.22 (s, 1H,OH); $^{13}$C NMR (100MHz,CDCl$_3$): $\delta$ 68.9, 89.7,120.0, 127.2, 129.6, 140.5, 159.5, 161.8, 162.8; MS: m/z =334(M$^+$); Anal. Calcd for C$_{10}$H$_7$ClN$_3$O: C, 32.22; H, 2.10; N, 12.52. Found: C, 31.90; H, 1.99; N, 12.40 %.

2.3.4. 2-(2-amino-1H-imidazol-4-yl)-4-chlorophenol (3d)
White solid, m. p. 270°C; Yield: 90 %; IR (KBr $\lambda_{\text{max}}$/cm$^{-1}$): 3568 (OH), 2924 (-NH), 1500 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$: 1.54 (s, 1H, NH), 1.48(s,2H,-CH$_2$), 6.56 (s,1H,NH), 7.11-7.47 (s, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 10.02 (s, 1H, OH); $^{13}$C NMR (100MHz,CDCl$_3$): $\delta$ 68.2, 117.7, 120.0, 122.0, 127.2, 129.6, 131.0, 159.7, 163.9, 165.8; MS: m/z =209 (M$^+$); Anal. Calcd for C$_{10}$H$_7$ClN$_3$O: C, 51.56; H, 3.85; N, 19.65 %.

2.3.5. 2-bromo-6-(2,5-dihydro-2-imino-1H-imidazol-4-yl)-4-methylphenol (3e)
White solid, m. p.: 285°C; Yield: 75 %; IR (KBr $\lambda_{\text{max}}$/cm$^{-1}$): 3588 (OH), 3568 (NH), 1531 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$: 2.11 (s, 3H, CH$_3$), 1.38(s, 2H, -CH$_2$), 7.16 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 10.83 (s, 1H, OH); $^{13}$C NMR (100MHz,CDCl$_3$) $\delta$: 26.7, 47.8, 114.2, 120.0, 122.3, 153.0, 153.9, 163.0, 164.8; MS: m/z =267 (M$^+$); Anal. Calcd for C$_{10}$H$_{10}$BrN$_3$O: C, 44.80; H, 3.76; N, 15.67. Found: C, 44.62; H, 3.22; N, 15.35%.

2.3.6. 2-(2,5-dihydro-2-imino-1H-imidazol-4-yl)-4-methyl-6-nitrophenol (3f)
White solid, m. p:220°C; Yield: 80 %; IR (KBr $\lambda_{\text{max}}$/cm$^{-1}$): 3543 (OH), 3105 (-NH),1512 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$:1.32 (s, 1H,NH), 1.45 (2,2H,-CH$_2$), 2.11 (s, 3H, CH$_3$), 6.84 (s, 1H, NH),7.79 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H); $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$: 26.7, 48.3,114.2, 120.0, 121.4, 136.3, 147.8, 154.5, 164.1,166.0; MS: m/z =234 (M$^+$); Anal. Calcd for C$_{10}$H$_{10}$N$_3$O$_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 50.94; H, 3.87; N, 23.35%.

2.3.7. 2-(2, 5-dihydro-2-imino-1H-imidazol-4-yl)-6-iodo-4-methylphenol (3g)
White solid, m. p.: 235°C; Yield:82%; IR (KBr $\lambda_{\text{max}}$/cm$^{-1}$): 3585 (OH), 3124 (-NH), 1558 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$: 1.18 (s, 1H, NH), 1.37 (s, 2H,-CH$_2$), 2.33 (s, 3H, CH$_3$), 6.7 (s, 1H, NH), 7.16 (s, 1H, Ar-H), 10.8 (s, 1H, OH); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$:
26.7, 50.0, 87.2, 120.0, 130.9, 133.7, 143.5, 157.1, 161.0, 163.2; MS: m/z = 314 (M⁺) Anal. Calcd for C₁₀H₁₀IN₃O: C, 38.12; H, 3.20; N, 13.34; Found: C, 37.96; H, 2.80; N, 13.15%.

2.3.8. 2-(-2, 5- dihydro 2-imino- 1H-imidazol-4-yl)-4-methylphenol (3h)
White solid, m. p.: 280⁰C, Yield: 87%; IR (KBr λmax/cm⁻¹): 3432 (OH), 3076 (-NH), 1527 (C=N); ¹H NMR (400MHz, DMSO-d₆) δ: 1.09 (s, 1H, NH), 1.52 (s, 2H, -CH₂), 2.72 (s, 3H, CH₃), 6.70 (s, 1H, NH), 7.35 (s, 1H, Ar-H), 7.11 (s, 1H, Ar-H), 10.65 (d, 1H, OH); ¹³C NMR (100 MHz,CDCl₃ ) δ: 26.7, 49.7, 114.2, 120.0, 130.9, 131.1, 131.9, 156.0, 161.9, 164.6; MS: m/z = 191 (M⁺) Anal. Calcd for C₁₀H₁₃N₃O: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.54; H, 6.48; N, 21.11%.

2.3.9. 2-(2,5-dihydro-2-imino-1H-imidazol-4-yl)benzene-1,3-diol (3i)
White solid, m. p: 304⁰C;Yield: 70%; IR (KBr λmax/cm⁻¹): 3527 (OH), 1546 (C=N); ¹H NMR (400MHz, DMSO-d₆) δ: 1.89 (s, 1H, NH), 1.72(s, 2H,-CH₂), 6.91 (s, 1H, NH), 7.96 (s, 1H, Ar-H), 8.06 (d, 2H, Ar-H),10.30 (s, 1H, OH), 11.02(s,1H, OH), ¹³C NMR (100 MHz,CDCl₃ ) δ: 64.3, 104.6, 109.6, 115.7, 131.0, 162.0, 162.9, 164.7, 165.0; MS: m/z =191(M⁺); Anal. Calcd for C₉H₉N₂O₂: C, 56.81; H, 4.7; N, 21.98. Found: C, 56.51; H, 7.40; N, 21.13%.

2.3.10. 4-(2, 5-dihydro-2-imino-1H-imidazol-4-yl)-6-iodobenzene-1,3-diol (3j)
White solid, m. p.: 310⁰C; Yield: 79%; IR (KBr) λmax/cm⁻¹: 3390 (OH), 1510 (C=N); ¹H NMR (400MHz, DMSO-d₆) δ: 1.47(s, 2H, -CH₂), 1.76 (s, 1H,NH), 6.17 (s, 1H, NH), 8.32 (s, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 10.81 (s,1H, OH), 11.08 (s, 1H, OH), ¹³C NMR (100 MHz, CDCl₃) δ: 63.5, 80.6, 104.6, 113.2, 140.0, 159.5, 162.0, 164.7, 166.9; MS: m/z = 316(M⁺) Anal. Calcd for C₉H₈I₂N₂O₂: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.54; H, 6.48; N, 21.11%.

2.3.11.4-(2,5-dihydro-2-imino-1H-imidazol-4-yl)-6-nitrobenzene-1,3-diol (3k)
White solid, m. p.: 210⁰C; Yield: 81%; IR (KBr λmax/cm⁻¹): 3395 (OH), 1520 (C=N); ¹H NMR (400MHz,DMSO-d₆) δ: 1.11 (s, 1H, NH), 1.36 (s,2H,-CH₂), 5.81 (s, 1H, NH), 7.29 (s, 1H, Ar-H), 7.32 (s, 1H, NH), 9.20 (s, 1H, OH), 9.56 (s, 1H, OH); ¹³C NMR (100MHz, CDCl₃) δ: 62.1, 102.9, 112.3, 125.9, 128.7, 160.0, 162.5, 167.0; MS: m/z = 236(M⁺) Anal. Calcd for C₉H₈N₄O₄: C, 45.77; H, 3.41; N, 23.10. Found: C, 45.35; H, 3.18; N, 23.00%.

2.3.12. 4-bromo-6-(2,5-dihydro-2-imino-1H-imidazol-4-yl)benzene-1,3-diol (3l): White solid, m. p.: 268⁰C; Yield: 88%; IR (KBr λmax/cm⁻¹): 3376 (OH),1590 (C=N); ¹H NMR
(400MHz, DMSO-d$_6$) δ : 1.23 (s, 2H, -CH$_2$), 1.70 (s, 1H, NH), 6.09 (s, 1H, NH), 7.54 (s, 1H, Ar-H), 8.10 (s, 1H, NH), 11.53 (s, 1H, OH), 11.86 (s, 1H, OH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ : 60.9, 106.4, 106.9, 115.3, 135.0, 163.0, 164.0, 165.9, 166.9; MS: $m/z = 268$ (M$^+$); Anal. Calcd for C$_9$H$_8$BrN$_3$O$_2$: C, 58.52; H, 5.40; N, 20.48. Found: C, 58.12; H, 5.23; N, 20.21%.

2.3.13. 2-(2,5-dihydro-1H-imidazol-4-yl)-5-methoxphenol (3m)

White solid, m. p.: 230$^0$C; Yield: 70%; IR (KBr λ$_{max}$/cm$^{-1}$): 3380 (OH), 1545 (C=N); $^1$H NMR (400MHz DMSO-d$_6$) δ : 1.05 (s, 1H, NH), 1.30 (s, 2H, -CH$_2$), 3.57 (s, 3H, OCH$_3$), 5.23 (s, 1H, NH), 7.21 (s, 1H, Ar-H), 7.30 (d, 2H, Ar-H), 10.83 (s, 1H, OH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ : 47.1, 55.2, 102.5, 113.0, 163.3, 164.5, 165.6, 167.0; MS: $m/z = 205$(M$^+$); Anal. Calcd for C$_{10}$H$_{11}$N$_3$O$_2$: C, 40.02; H, 3.99; N, 15.56. Found: C, 39.35; H, 3.20; N, 15.01%.

2.3.14. 2-(2,5-dihydro-1H-imidazol-4-yl)-4-iodo-5-methoxphenol (3n)

White solid, m. p.: 260$^0$C; Yield: 86%; IR (KBr λ$_{max}$/cm$^{-1}$): 3190 (OH), 1550 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) δ : 1.43 (s, 1H, NH), 1.76 (s, 2H, -CH$_2$), 3.05 (s, 3H, OCH$_3$), 5.67 (s, 1H, NH), 7.21 (s, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 10.83 (s, 1H, OH); $^{13}$C NMR (400 MHz, CDCl$_3$) δ : 49.2, 55.2, 102.5, 112.8, 140.5, 161.0, 163.5, 164.0, 164.9; MS: $m/z = 330$(M$^+$); Anal. Calcd for C$_{10}$H$_{10}$I$_3$O$_2$: C, 36.27; H, 3.04; N, 20.48. Found: C, 36.05; H, 2.90; N, 20.20%.

2.3.15.2-(2,5-dihydro-1H-imidazol-4-yl)-5-methoxy-4-nitrophenol (3o)

White solid, m.p.: 260$^0$C; Yield: 75%; IR (KBr λ$_{max}$/cm$^{-1}$): 3263 (OH), 1581 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) δ : 1.50 (s, 1H, NH), 1.64 (s, 2H, -CH$_2$), 3.37 (s, 3H, OCH$_3$), 5.49 (s, 1H, NH), 8.26 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 11.80 (s, 1H, OH); $^{13}$C NMR δ: (100 MHz, CDCl$_3$) δ : 49.2, 55.2, 102.5, 113.0, 126.1, 126.5, 161.0, 162.3, 164.4, 168.0; MS: $m/z = 250$(M$^+$); Anal. Calcd for C$_{10}$H$_{10}$N$_3$O$_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.87; H, 3.77; N, 22.10%.

2.3.16. 4-bromo-(2,5-dihydro-1H-imidazol-4-yl)-5-methoxphenol (3p)

White solid, m. p.: 309$^0$C; Yield: 73% IR (KBr λ$_{max}$/cm$^{-1}$): 3091 (OH), 1509 (C=N); $^1$H NMR (400MHz, DMSO-d$_6$) δ : 1.26 (s, 1H, NH), 1.40 (s, 2H, -CH$_2$), 2.81 (s, 3H, OCH$_3$), 5.09 (s, 1H, NH), 7.14 (s, 1H, Ar-H), 7.32 (s, 1H, NH), 8.43 (s, 1H, OH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ : 51.3, 56.1, 106.4, 106.9, 115.3, 135.0, 160.2, 161.0, 163.1, 165.1, MS: $m/z =$
283(M+); Anal. Calcd for C_{10}H_{19}BrN_{3}O_{2}: C, 42.27; H, 3.55; N, 14.79. Found: C, 47.07; H, 3.21; N, 14.55%.

3. RESULTS AND DISCUSSION

3.1. Optimization of reaction conditions

Initially, 1d was chosen as a model substrate. To optimize the reaction conditions in various solvents at different time intervals, 1d was reacted with guanidine carbonate to afford 2-(2-imino-1H-imidazol-4-yl)-4-chloro phenol 3d. Scheme 1, Table 1.

Table 1: Effect of different solvents for the synthesis of 3d under ultrasound irradiation at 80°C

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solvent + Catalyst</th>
<th>Yield (%) / Time (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Thermal: Sonication</td>
</tr>
<tr>
<td>S₁</td>
<td>ethylene glycol</td>
<td>0/12: 0/4</td>
</tr>
<tr>
<td>S₂</td>
<td>DMF/ piperidine/pyridine</td>
<td>35/8: 45/4</td>
</tr>
<tr>
<td>S₃</td>
<td>EtOH/ I₂/NaOH</td>
<td>40/12: 50/4</td>
</tr>
<tr>
<td>S₄</td>
<td>Acetonitrile</td>
<td>65/16: 76/4</td>
</tr>
<tr>
<td>S₅</td>
<td>[bmim]BF₄</td>
<td>70/6: 85/2</td>
</tr>
<tr>
<td>S₆</td>
<td>[bmim]BF₄/Acetonitrile</td>
<td>75/6: 90/2</td>
</tr>
</tbody>
</table>

The reaction of 1d in ethylene glycol S₁ at reflux displayed no conversion to 3d within 12 hrs. Reaction time was carefully regulated to avoid the decomposition of products and formation of by products. It was observed that reaction proceeded well in ethanol with catalytic amount of NaOH, S₃ at reflux and was complete within 12 hrs, giving 3d in 40% isolated yield. Further reaction in DMF/ piperidine/pyridine, S₂ at reflux for 8 hrs reduced the yield. The efficiency of reaction was markedly influenced by the nature of solvents was noticed in S₄ acetonitrile, the yield was improved to 65%. The reaction in [bmim][BF₄], S₅ showed 70% yield where as 75% yield was observed in [BMIM][BF₄]/ ACN, S₆.

On sonication, increase in the efficiency of reaction with the output of 45%, 50%, 76%, 85%, 90% yields were observed in S₂-S₆ respectively reduced times attested for the acceleration of the rate of electron transfer reactions. This implies that “sono-thermal” decomposition of the solvent inside the cavity does not occur and higher selectivities could
possibly be obtained leading to significant improvements in yield and reaction time due to mass transfer enhancement $^{[58-60]}$.

We have conducted our reactions in Ultrasonic Cleaner (Sm 200 US), (with a temp range up to 80°C for continuous process), the frequency was set at 20 kHz and 35 kHz with a fixed amount of [BMIM][BF$_4$]/ACN (0.5: 30 mmol). The yields for the reactions corresponding to 20 kHz and 35 kHz were 82% and 90% respectively. We have optimized the reaction conditions at 35 kHz.

Overall, the use of [bmim][BF$_4$], $S_5$ resulted in much higher reaction rates than those performed in $S_1$-$S_4$ solvent systems. Remarkably, it was observed that the reaction of 1d proceeds better in [BMIM][BF$_4$], $S_5$ and [BMIM][BF$_4$]/ACN, $S_6$ as compared to common organic solvents $S_1$-$S_4$. Reaction in $S_6$ unquestionably showed the highest levels of efficacy and atom economy when compared to solvents $S_1$-$S_4$ in thermal as well as sonochemical modes of reaction. In addition, use of ionic liquid with acetonitrile decreased the vapour pressure and viscosity of acetonitrile and ionic liquid respectively.

Table 1 summarizes our results, clearly showing the superiority of [bmim][BF$_4$]/ACN solvent system over other organic solvents. The course of the reaction was monitored by TLC but we found that for all early experiments, TLC or HPLC was not an optimal choice for evaluation of yields or for a quantitative in-process assay; the viscous solution containing acetonitrile and ionic liquids was not conductive to TLC. We resorted to quenching the reaction and isolating product. Elemental analysis on isolated compounds were used to confirm product formation and yields were calculated on purified compounds.

We extended our investigation to other substrates by varying the substituents on ring A Table 2.

Table 2: Synthesis of substituted 2 imino-4, 5-dihydro-imidazole (3a-p) promoted by ultrasound irradiation at 35 kHz

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>R$_3$</th>
<th>Yield$^{ab}$ (%)</th>
<th>M.P. (°C)</th>
<th>Mol. Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Cl</td>
<td>H</td>
<td>Br</td>
<td>40/89</td>
<td>290</td>
<td>C$_9$H$_9$BrClN$_3$O</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Cl</td>
<td>H</td>
<td>NO$_2$</td>
<td>45/85</td>
<td>225</td>
<td>C$_9$H$_9$ClN$_3$O$_3$</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Cl</td>
<td>H</td>
<td>I</td>
<td>48/82</td>
<td>276</td>
<td>C$_9$H$_9$ClI$_3$O</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>55/90</td>
<td>270</td>
<td>C$_9$H$_9$ClN$_3$O</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>CH$_3$</td>
<td>H</td>
<td>Br</td>
<td>51/80</td>
<td>285</td>
<td>C$_9$H$_9$ClN$_3$O</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>CH$_3$</td>
<td>H</td>
<td>NO$_2$</td>
<td>39/80</td>
<td>220</td>
<td>C$<em>{10}$H$</em>{10}$N$_4$O$_3$</td>
</tr>
</tbody>
</table>
The incorporation of electron withdrawing substituents at the various position of ring A (entries 3a-g, j, k, l, n) resulted in increased yields. Electron donating substituents at ring A decreased yields. Table 2 reveals that, the substrates containing more than two electron withdrawing groups at various positions of ring A resulted in increased efficiency of the reaction due to synergistic effects.

To verify the impact of concentration of [bmim][BF₄] on the efficiency of the reaction, we gradually increased the concentration of [BMIM][BF₄]/ACN from 2.5mmol, 5.0mmol, 7.5mmol and 10mmol keeping 30 mmol of ACN constant at 80°C for 2 h (Table 3).

Table 3: Effect of molar concentration of [bmim][BF₄] ionic liquid verses ACN at 80°C on the formulation of 2-(2-imino-1H-imidazol-4-yl)-4-chlorophenol (3d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>[BMIM][BF₄] (mmol)</th>
<th>ACN (mmol)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 (0.56mL)</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>5.0(1.1mL)</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>7.5(1.6mL)</td>
<td>30</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>10(2.2mL)</td>
<td>30</td>
<td>65</td>
</tr>
</tbody>
</table>

As the concentration of [BMIM][BF₄] in ACN increased, the efficiency of the reaction decreased at 7.5mmol and above. Variations in yield prompted us to repeat this procedure several times; proving that variations in yield were not attributable to work-up losses. Beyond 7.5 mmol of [BMIM][BF₄] the efficiency was decreased: Increased viscosity of ionic liquid retards the sonochemical reaction due to inhibition of cavitation process.
3.2. Effect of time on ultrasonic irradiation: The yield of substituted imidazoles depends on ionic liquid, the ultrasonic irradiation time, and the ultrasonic frequency. The ultrasonic irradiation time had significant effect on the condensation, when the amount of IL (0.5 mmol) and the ultrasonic frequency (35 kHz) were kept constant. The sonication process was conducted at time intervals of 30, 60, 90, 120, 150, 180 minutes. 10%, 40%, 65%, 90% yields of 3d were obtained at 30, 60, 90, 120 minutes respectively. Excellent conversion was observed at 120 mins. No conversion was observed beyond 120 min. An increase in the reaction time, directly, leads to the increase in yields of compound 3d.

3.3 Plausible Mechanism for Acceleration: In classical synthesis of imidazoles, the reaction is initiated by formation of halo ketones. Guanidine reacts with carbonyl functionality to furnish imines; the reaction proceeds via dehydrohalogenation cyclocondensation. We were unable to isolate guanidine as free base; we developed a one pot procedure to ameliorate this problem. The first step required halogenations of acetophenone at the methyl carbon resulting in formation of phenacyl bromides. Reaction with guanidine carbonate leads to formation of an intermediate, dehydration of the labile compounds leads to energetically stable imidazoles. Initially the reactions were carried out in various solvents like ethanol, DMF/piperidine/pyridine system, acetonitrile and [BMIM][BF₄] using molecular Br₂ in catalytic amount under reflux for 6 to 16 hrs. The time factor and yield were always a matter of concern in conventional method.

![Figure 1: A plausible reaction mechanism for [BMIM][BF₄]/ACN solvent system under sonication](image-url)
Sonochemical reactions in ionic liquids non-aqueous system furnish interesting acoustic vibrations and effects of cavitation on increase in the rates and selectivities of most chemical reactions in ultrasonic fields. Interestingly, [BMIM][BF₄] /ACN solvent system proved to be exceptionally effective in enhancing the efficiency of the reaction under ultrasound irradiation. Diagrammatic representation of the mechanism is depicted in Figure 1.

Our study clarifies the assistance of ultrasound irradiation to accelerate the rate of reaction. The difference in yields and reaction times may be a consequence of the specific effects of ultrasound. The effect observed on the reaction is due to the phenomenon of acoustic cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer and allowing chemical reactions to occur swiftly [61]. In response to sound field, fluid tends to move faster than solid particles due to its relatively low density. As a result, a low pressure region is created on the reaction mixture surfaces in the rarefaction cycle of the sound. Cavitations bubbles form at the crevices on the solution surface and collapse locally when the compression cycle of wave arrives. This rapid collapse of bubbles induces very strong shear flows which enhance mixing and mass transfer in the solution and increase reaction area [62-65]. The sonochemistry mechanism also facilitates the formation of very reactive chemical species having short lifetime that promotes the rapid synthesis of imidazoles via both phenacyl bromide and imine formation. A plausible mechanism involved in cyclocondensation reaction for the synthesis of imidazole can be outlined as follows: phenacyl bromide (C) reacts with one molecule of guanidine in [BMIM][BF₄]/ACN to form Schiff base (D) which undergoes dehydrohalogenated cyclocondensation. Thus formed imines (D) via subsequent cyclization afford the final product (E), i.e., imidazole. Interestingly, reduced reaction time and improved yield were observed, this implies that the reaction may proceed via free radical mechanism with rapid generation of reactive intermediate (B) followed by formation of halo ketone (C) which in turn reacts with guanidine. Ultrasonic irradiation may accelerate the rate of reaction in imine (D) formation. On completion of the reaction, we optimized the extraction and isolation of the resulting product in ionic phase by using diethyl ether. The separated ionic liquid was flushed out with diethyl ether, vacuum dried and reused directly without further purification without diminution of the yields up to the 5 cycle but there is noticeable drop in yield after 5th cycle suggesting that the [BMIM][BF₄] may have been contaminated, degraded or exhausted Table 4. Our protocol has the merit of being...
environmentally benign, possessing simple operation, convenient work-up, reduced time and proceeding in good yields.

**Table 4:** Recycling effect of [BMIM][BF₄] on the formulation of 2-(2-imino-1H-imidazol-4-yl)-4-chlorophenol (3d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Recycling</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>60</td>
</tr>
</tbody>
</table>

**3.4 Compound Characterization and Structure Elucidation:** For compounds 3a–p (Table 2), the infrared spectra showed a broad peak at 3568 cm⁻¹ owing to OH and NH stretching of the phenyl and imidazole ring respectively; disappearance of C=O peak indicated the formation of ring imidazole. A peak at 3120 cm⁻¹ was attributed to NH proton typical of imidazoles ring. ¹H NMR spectra of compound 3a-3h and 3m-3p showed singlets at δH 10.4 to δH 11.5 ppm for OH group. Two singlets at δH 11.02 and δH 10.3 ppm could be assigned to OH groups of compounds 3i-3l respectively. The ¹H NMR spectra of compounds 3a-3p displayed additional signals at δH 6.9–NH linkage derived from imidazole ring, while the signal due to the =NH group of imino imidazole ring appeared at δH 1.2 ppm. In addition, the three protons of the methoxy group in compounds 3m-3p resonated as a singlet at δC 3.78–3.87 ppm. The ¹³C NMR spectra also support the structures of the products: 3d showed peaks at δC 117.7, 120.0, 122.0, 127.2, 129.6, 131.0, 159.7, 8 ppm and compounds 3a-3p revealed peaks at δC 163.9, 165 and 68.2 ppm indicating the presence of imidazole ring. Satisfactory elemental analyses were obtained for compounds 3a–p, and the mass spectral data also lent credence to the assigned structures (Table 1).

**5. CONCLUSION**

Ultrasound irradiated synthesis of imidazolines in ionic liquid [BMIM][BF₄]/ACN at 80° C within 2 h proved to be exceptionally efficient. [bmim][BF₄] can be reused up to 5th cycle but after the 5th loss of its activity has been observed. Ultrasonic frequency has an impact on reaction yield: increasing the frequency of from 20 kHz to 35 kHz, increase yield of 3d from
82% to 90%. The ultrasonic irradiation time has also considerable effect on reaction yield; excellent conversions were observed at 2 h. Ultrasonication also accelerates transformations, such as cyclization and dehydration. The attractive features of this protocol are simple procedure, high selectivity, short reaction time, use of cheap and environmentally benign solvent, and the reusability of ionic liquid.

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REFERENCES