NOVEL BRONSTED ACIDIC IONIC LIQUID L-PYRROLIDINE-2-CARBOXYLIC ACID SULFATE: AN EFFICIENT AND ECO-FRIENDLY CATALYST FOR SYNTHESIS OF 2,4,5-TRISUBSTITUTED-1*H*-IMIDAZOLES UNDER SOLVENT FREE CONDITIONS

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A simple, highly efficient and eco-friendly protocol for the synthesis of bioactive 2,4,5-trisubstituted-1*H*-imidazoles via one-pot three component condensation of benzil, aromatic aldehydes and ammonium acetate under solvent free conditions has been achieved utilizing the novel Bronsted acidic ionic liquid, (L-pyrrolidine-2-carboxylic acid sulfate) as catalyst. The distinguishing features of this methodology are excellent yields in shorter reaction time, cleaner reaction profile, and environmentally friendly nature, use of non-toxic, easily synthesizable, inexpensive catalyst.

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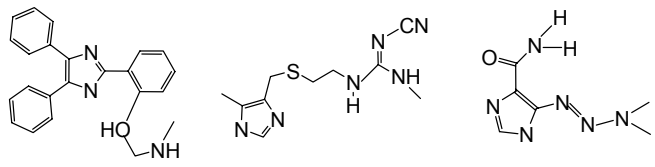
Introduction

Heterocyclic compounds containing imidazole moiety have many pharmacological properties and play an important role in biochemical processes. Highly substituted imidazoles are the key intermediates in the synthesis of various therapeutic agents and act as a subunit in drugs such as Olmesartan, Losartan, Eprosartan (angiotensin II receptor antagonist), Metronidazole (antibiotic), Trifenagrel (platelet aggregation inhibitor), Dacarbazine (antineoplastic), Cimetidine (H_2-receptor antagonist) (Figure 1), methimazole (antithyroid), Pilocarpine (muscarinic receptor agonist), Etomidate (intravenous anesthetic) as well as plant growth regulators,[1] fluorescence labeling agents, biological imaging[2] and chromophores for non-linear optic systems. These moieties have been reported as antibacterial, anti-inflammatory, antihypertensive, antithrombotic, fungicidal,[3] antiallergic, antiviral[4] and herbicidal properties. On the other hand an ionic liquid catalyzed reaction have gained considerable attention because of their interesting properties like high thermal stability, non volatility, eco-friendly benign nature and reusability leading to proceed the reaction effectively with high yields in shorter reaction times.

In view of the diverse pharmacological properties of these potent compounds, many methodologies have been developed using various catalytic systems such as InF_3,[5] $InCl_3.3H_2O$,[6] $BF_3.SiO_2$,[7] $Zr(acac)_4$,[8] I_2,[9] TBAB,[10], CAN,[11] DABCO,[12] $Yb(OTf)_3$,[13] L-proline,[14] zirconium(IV)-modified silica gel,[15] p-TSA,[16] Wells–Dawson heteropolyacid,[17] MCM-41-SO_3H,[18] p-dodecylbenzenesulfonic acid, cellulose sulfuric acid,[19] silica-bonded sulfonic acid, boric acid[20] and ammonium metavanadate.[21] Ionic liquid catalyzed reactions were also reported using [EMIM]OAc,[22] $[Et_3NH][HSO_4]$,[23] [HeMIM]BF_4,[24] $[(CH_2)_4SO_3HMIM][HSO_4]$,[25] and triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate. Recently sulphated tin oxide,[26] poly ethylene glycol,[27] and molecular iodine[28] were also used efficiently for this reactions. However, many of these reported methods suffer from one or several drawbacks such as low yields, prolonged reaction times, use of toxic, costly, moisture-sensitive, excess quantity of reagents, harsh reaction circumstances, special apparatus, difficult workup procedure and difficulty in recovery and reusability of the catalysts. Therefore, still there is a need to build up an efficient, eco-friendly and easy method for the synthesis of imidazole derivatives.



Trifenagel Cimetidine Decarbazine

Figure 1. Physiologically highly active substituted imidazole derivatives.

With respect of our efforts to develop Brønsted acidic ionic liquid catalyzed synthetic methodologies, we report here in a simple, highly efficient and eco-friendly method for the synthesis of 2,4,5-trisubstituted-1H-imidazoles under solvent-free conditions (Scheme 1) in excellent yields utilizing an inexpensive novel Brønsted acidic ionic liquid, pyrrolidine-2-carboxylic acid sulphate (IL), as catalyst.

Table 1. Synthesis of 2,4,5-trisubstituted-1H-imidazole (**2a-i**).

S.	Aldehyde	Time	Yield (%)	Melting point (°C)	
				Observed	Reported
2a	Benzaldehyde	90	80	271 - 273	270 - 272
2b	2-Hydroxy benzaldehyde	180	85	205-206	204-207
2c	4-Nitro bennzaldehyde	45	75	241-243	242-243
2d	4-Chloro benzaldehyde	30	75	260-262	261-263
2e	4-Methoxy benzaldehyde	180	75	230-232	231-233
2f	1-Naphthaldehyde	90	82	240-242	242-243
2g	4-Dimethylamino benzaldehyde	45	75	256-257	256-258
2h	2-Hydroxy 1-naphthaldehyde	90	75	188	---
2i	9-Anthraldehyde	90	80	222	---

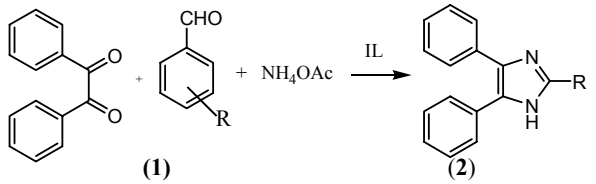
Experimental

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were obtained by using Digital melting point apparatus EQ730 (Equiptronics) and are uncorrected. The progress of the reactions and purity of product formation were monitored by thin layer chromatography using hexane/ethyl acetate ((8/2) as eluent. The products were characterized by comparing with authentic samples and spectroscopic data (IR, ^{1}H NMR). IR spectra were recorded on Schimadzu IR Solution 150SUI spectrophotometer using KBr pellet, values are expressed in cm^{-1}. NMR spectra were recorded on Bruker 400 MHz spectrometer using appropriate solvent and TMS as an internal standard, chemical shift are expressed in ppm. Mass spectra were measured on a Jeol JMSD-300 spectrometer. Viscocity was measured by Buckfield CPe40.

Results and discussion

2,4,5-Trisubstituted-1H-imidazoles (**2a-i**) were synthesized by condensing benzil with various aldehydes (**1a-i**) and ammonium acetate at 100 ^{0}C using IL as a catalyst (Scheme 1). The results were reported in Table 1.

The efficiency of IL catalyst has been determined and compared with those of reported acid catalysts in the synthesis of 2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (**2d**). The results showed that IL is more efficient as a catalyst in terms of product yields and reaction times (Table 2). All the newly synthesized compounds were characterized by their analytical and spectroscopic data (IR, ^{1}H NMR) and the known compounds were confirmed by comparing their m. p. with authentic samples.



Scheme 1. Synthesis of substituted imidazoles.

Synthesis of a pyrrolidine-2-carboxylic acid sulphate

A mixture of L-proline and conc. sulphuric acid in appropriate amount was stirred for 24 h in a round bottom flask. The viscous liquid obtained was stored in dry container.

Synthesis of 2,4,5-trisubstituted-1H-imidazoles (4a-i)

To a mixture of benzil (1 mmol), aromatic aldehyde (1 mmol) and ammonium acetate (3 mmol), IL in catalytic amount (0.1 mmol) was added and stirred at 100 ^{0}C for an appropriate time as indicated in table 1. After completion of the reaction, as monitored by TLC, 10 mL of water was added and stirred at room temperature for further 10 min. The separated solid was filtered, washed with excess water, dried and recrystallized from ethanol to afford pure product in good yield.

Spectral studies

L-Pyrrolidine-2-carboxylic acid sulfate catalyst.

Golden yellow colour, b. P. 272 °C. ES-MS *m/z* (%): 231 (M+H). Viscocity: 3.06 CP. IR (KBr): 3510 (OH), 3410(NH), 3005(CH_2), 1514(N-H),1788(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.32(1H, m, 8.20 Hz), 3.41-3.17(2H, m, 6.20 Hz), 2.23-2.290 (2H, m, 6.20 Hz), 2.27-2.50 (2H, m, 6.40 Hz, 8.70 Hz), 1.86-1.99(2H, m, 6.40 Hz, 6.20 Hz),9.31(1H, acidic proton), 8.68(2H, N-H, Proton).

*2,4,5-Triphenyl-1H-imidazole (**2a**)*

White Solid, m.p. 271-273°C. ES-MS *m/z* (%): 297 (M+H). IR (KBr): 3149 (NH), 1610(C=N), 1537(C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.54 - 8.09 (m, 5H), 7.20-7.51 (m, 10H)12.17 (s, 1H).

*2-(Anthra)-4,5-diphenyl-1H-imidazole (**2i**).*

Yellow solid. IR (KBr): 3005 (NH), 1602 (C=N), 1537 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.24-7.31 (m, 2H), 7.40-7.43 (m, 4H), 7.54(m,1H) , 8.16 - 8.19 (m, 4H), 7.91-7.93(m, 4H), 12.92 (s, 1H). ES-MS *m/z* (%): 396 (M+H).

Table 2. The effect of catalyst on reaction.

S. No.	Catalyst	Time (min)	Yield (%)
1	No catalyst	600	Traces
2	P-TSA	120	68
3	Sulphamic acid	90	82
4	Sulphanilic acid	70	85
5	IL Catalyst	30	90

Conclusion

In conclusion, we have derived a simple, highly efficient and environmentally friendly protocol for the synthesis of 2,4,5-tri-substituted-1*H*-imidazoles by one pot three component condensation of benzil, aromatic aldehydes, and ammonium acetate utilizing inexpensive and eco-friendly Bronsted acidic ionic liquid as a catalyst.

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