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A PERCHLORIC POLYBORATE: REUSABLE GREEN CATALYST PROMOPTED ONE-POT SYNTHESIS OF TRISUBSTITUTED IMIDAZOLES UNDER SOLVENT-FREE CONDITIONS VIA A DOMINO SEQUENTIAL FACILE MULTICOMPONENT REACTION

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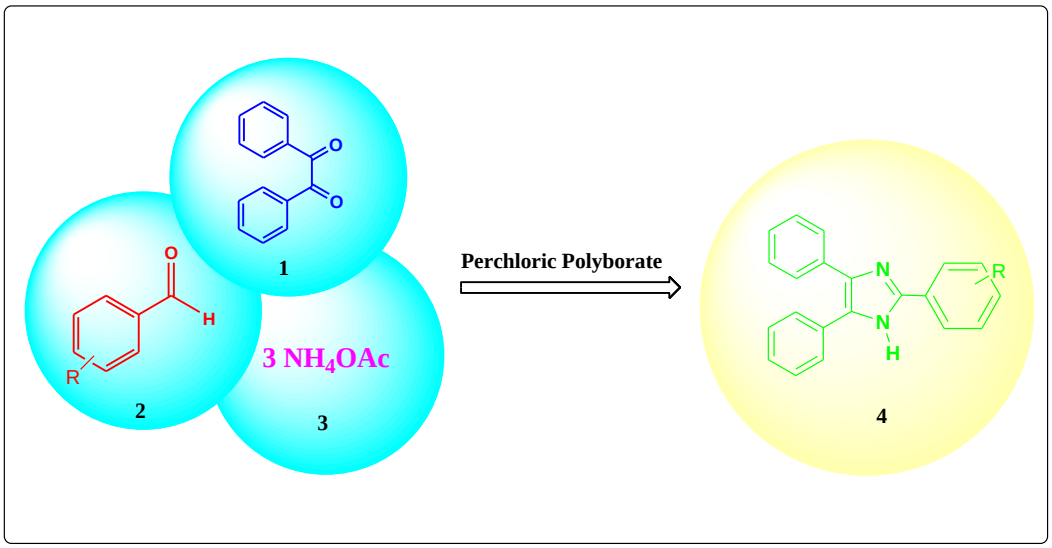
ABSTRACT:

In the present work a novel catalyst has been synthesized and employed as a highly efficient catalyst for a green three component one pot condensation of substituted aromatic aldehydes, benzil and ammonium acetate to give 2,4,5-trisubstituted imidazoles. The structure of catalyst was investigated through analytical techniques such as scanning electron microscopy, X-ray diffraction, Fourier transform Infrared spectroscopy and energy dispersive X-ray spectroscopy were used for catalyst characterization. The overall methodology shows salient features such as low loading of catalyst, short reaction time, easy separation and purification of the products, low cost make this procedure economically attractive and highly suitable eco-friendly protocols. Products were investigated by proton nuclear magnetic spectroscopy, carbon nuclear magnetic spectroscopy, fourier transform infrared spectroscopy and high resolution mass spectroscopy.

KEYWORDS: 2,4,5-trisubstituted imidazoles, perchloric polyborate, imidazoles, solvent-free, green chemistry.



INTRODUCTION:

N-based heterocyclic compound have various application in the fields of polymer, drug discovery, material science, medicinal, organometallic catalysis, ionic liquid formation industrial application in pharmaceutical fields and bioactive application such as it is used as anti-metastatic agents, imidazolium hydrogels and antiarrhythmic[i]. It is used as a chiral auxiliary in enantioselective reactions and valuable role in modern organic synthesis and synthetic application including Henry reactions, Suzuki-Miyaura coupling reactions, Michael reactions, Mannich reactions, Mizoroki-Heck reactions and Friedel-craft reaction in which imidazolines catalyst shows enantioselective excellent activity and it is used in agrochemicals to recent research in to solar cells and other optical application[ii-iii].

Imidazole-containing molecules are used to inhibit P38MAP kinase, plant growth regulators, herbicides, antithrombotic agents, anti-inflammatory agents, therapeutic agents, fungicides and its derivatives plays valuable medicinal role such as enzyme inhibition, antihistaminic, antibacterial, anticancer, antifungal, anti-inflammatory, antiviral, anti-parasitic, anti-allergic, antimicrobial, antiulcer, anticancer, analgesic, anti-inflammatory, antiviral, anticonvulsant, anthelmintic, histamineH_3anatogmist, antimalarial, antioxidant, afarnesyltransferase and eranylgeranyltransferase-I inhibitor, antitumoral, antiprotozoal, antidiabetic activity and its analog place important role in medicine such as Ronidazole, Dimetridazole, Azathioprine, Carnidazole, Mizoribine and Mezlocillin[iv-v]. Solvent free reactions and solid phase synthesis using appropriate catalyst minimize formation of byproduct in reaction offers excellent green protocol for various trisubstituted imidazoles derivatives[vi].

Boric acid dehydrates above 100^{o}C and converts to its polymeric forms which possessing active species catalyzing the reaction in this process liberates water molecules which may hamper the progress of reaction so boric acid was dehydrated at 200^{o}C to convert it into its polymeric Lewis acid form and then sulfonated to introduce mild Brönsted acid character. Boron being an electron deficient and electron withdrawing effect of adjacent sulfate enhance its Lewis acidity hence it has both Lewis as well as Bronsted acid character[vii]. Polymeric Lewis acid form of boric acid supported with aluminium. Aluminum being an electron-deficient element, hence it has good Lewis acid character[viii]. Aluminized and sulfated polyborate suitable catalytic application in various multicomponent reactions[ix-xiii].

Inspired with this to prepare newer catalyst which represent excellent catalytic activity in multicomponent reactions. Now a day solid supports catalyst is emerging field which is easier way for purification methodology and preventing reaction residue into climate. Thus solvent-

free condition and supported perchloric acid environmental bengin protocol for green synthesis which includes $HClO_4$/PANI, $HClO_4$-C, SBA-15/$HClO_4$[xiv-xvi].

In general, the trisubstituted imidazole are synthesized by a one pot three component reaction of aldehyde, benzil and ammonium acetate using variety of catalytic systems such as $BiFeO_3$/$CuWO_4$[xvii], Fe_3O_4@g-C_3N_4[xviii], Benzethonium Chloride[xix], Citrate trisulfonic acid (CTSA)[xx], wet cyanuric chloride[xxi], diethyl ammonium hydrogen sulfate[xxii], iodine/DMSO[xxiii], SiO_2/Fe_3O_4/SO_3H[xxiv], sodium lauryl sulfate (SLS)[xxv,] [2-(imm)-4-{b(immh)m}c][HSO_4]$_3$[xxvi], Fe_3O_4-DOPA-Cu[xxvii], Fe_3O_4/SO_3H@zeolite-Y[xxviii], $CuFe_2O_4$@Si-Imid-PMo[xxix], {C_2H_4[P(C_6H_5)$_3$]$_2$}{Mo_6O_{19}}·SO (CH_3)$_2$[xxx], [P_4-VP]-Fe_3O_4[xxxi], lactic acid[xxxii], (CTA)$_3$PMo-MMT nanocomposite[xxxiii], Urea and PPh_3[xxxiv], Tin oxide plant assisted nanoparticle[xxxv], 3-picolinic acid[xxxvi], nano-Fe_3O_4@ZrO_2 supported PMA[xxxvii], Acetic acid functionalized poly(4-vinylpyridinium) bromide[xxxviii], HMS-SA[xxxix], $H_3PW_{12}O_{40}$-amino-functionalized $CdFe_{12}O_{19}$@SiO_2 nanocomposite[xl], Ti^{4+}/4 Å MS[xli], Pyridine-2-carboxylic acid[xlii], Cu/C [xliii], Acidic Ionic Liquid [H-NP]HSO_4[xliv], $NiFe_2O_4$@SiO_2@glucoseamine MNPs[xlv], silica-supported $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles[xlvi], GO/CA[xlvii], Fe_3O_4 magnetic nanoparticles (Fe_3O_4 MNPs)[xlviii], Fe_3O_4@PVA-SO_3H[xlix], $CoFe_2O_4$@SiO_2-SO_3H[l], ZnS-$ZnFe_2O_4$[li], Fe-DTPMP[lii], PMO@ILBF_4[liii], rGO-NiO-NCs[liv], White LED[lv], Cu/C NPs[lvi], Water extract of pomelo (WEP)[lvii], MCS-GT@Co(II)[lviii], A-MFGO[lix], Nanosilica-supported Imidazolium Ionic Liquid[lx], (CTA)$_3$PMo-MMT[lxi], Fe_3O_4@chitosan nanoparticles[lxii], Fe_3O_4@SiO_2-EP-HEAF[lxiii]**.**

Figure I indicate the biologically active imidazole derivatives [xxxiv].

All these literatures reported methods along with some important features may also suffer from one or more limitations such as use of expensive catalyst, drastic reaction condition, low product yield, tedious workup procedure, need of column purification, etc. Under ultrasonic irradition or microwave, classical conditions or solvent-free. Therefore there is still a demand to develop newer protocols for the synthesis of trisubstituted using green chemistry approach. With this background and in continuation to our research work herein we wish to report an application of perchloric polyborate as a green catalyst for environmentally benign synthesis of trisubstituted imidazole by using variously substituted aldehydes, benzil and ammonium acetate at 140^{o}C under solvent free condition.

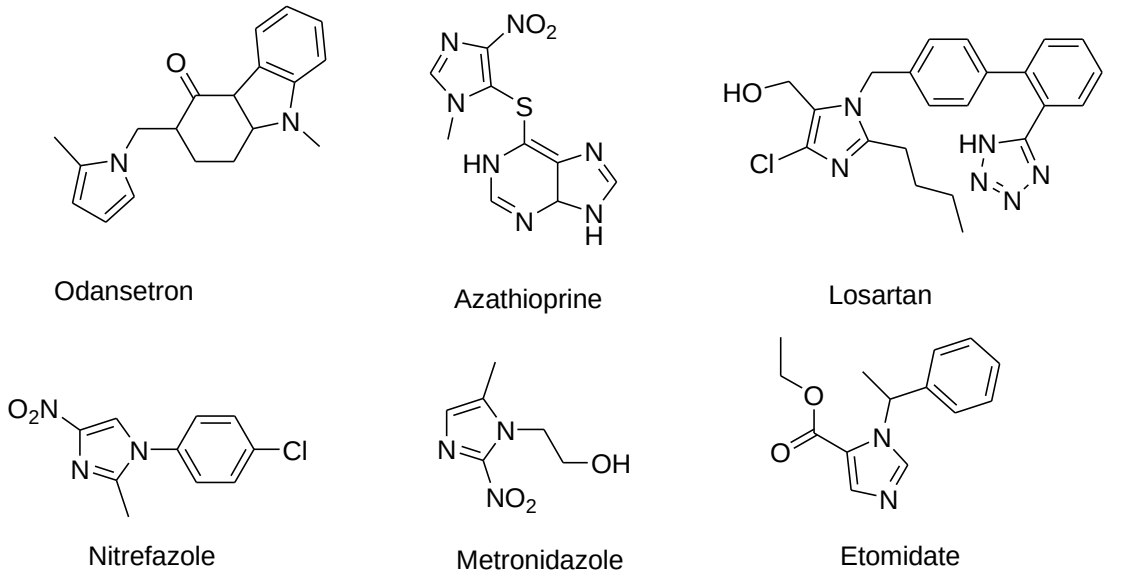
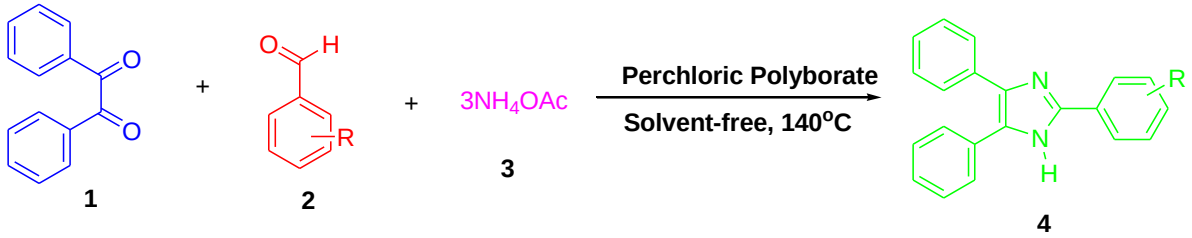


Figure I: Biologically active imidazole derivatives

RESULT AND DISCUSSSION:

The reaction was carried out by mixing substituted aromatic aldehydes (1 mmol), benzil (1 mmol) and ammonium acetate (3 mmol) in presence perchloric polyborate (75 mg) as a

homogenous green solid acid catalyst. The reaction mixture was optimized at different solvents condition. The model reaction between 4-methoxy benzaldehyde, benzil and ammonium acetate in presence of perchloric polyborate catayst was used to study the effects of solvents on synthesis of trisubstituted imidazoles derivatives. The ideal conditions for the synthesis of trisubstituted imidazole derivatives were solvent-free.



Scheme I: Synthesis of trisubstituted imidazoles

Table 1 Effect of solvent on synthesis of trisubstituted imidazoles derivatives

Entry	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1	Solvent-free/ Grinding	RT	5	-
2	Solvent-free	80°C	5	-
3	EtOH	Reflux	10	-
4	Solvent-free	100-110°C	10	-
5	1 : 1 EtOH/H_2O	Ultrasonication	15	-
6	EtOH	Ultrasonication	15	-
7	Solvent-free	130°C	25	85
8	Solvent-free	140°C	25	91

Initially the model reaction was carried out in various solvents like H_2O, EtOH, DMF, THF and CH_3CN as well as under solvent free condition using the perchloric polyborate catalyst at different temperature as shown in (Table 1). The result indicates that, the reaction works smoothly with good to excellent product yields, short reaction time and no side reaction at 140°C under solvent free condition.

Table. 2 Effect of amount of catalyst on synthesis of trisubstituted imidazoles derivatives

Entry	Catalyst amount (gm)	Time (min)	Yield (%)
1	0	25	Trace
2	0.025	25	33
3	0.050	25	67
4	0.075	25	91
5	0.100	25	90

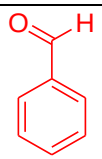
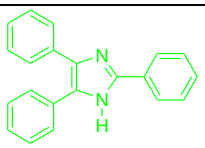
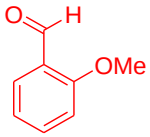
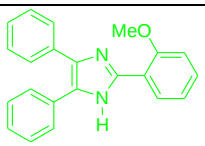
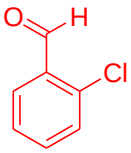
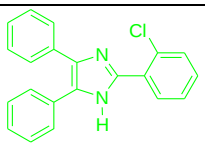
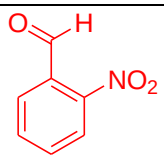
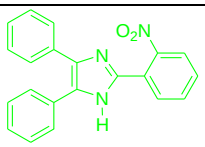
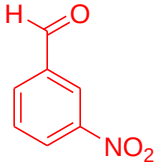
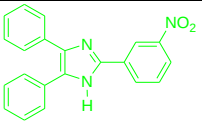
The model reaction between 4-methoxy benzaldehyde, benzil and ammonium acetate under solvent-free condition at 140°C was carried out in the presence of perchloric polyborate catalyst. Under the above optimized condition a model reaction was carried out using different amount of catalyst like 0.025gm, 0.050gm, 0.075gm and 0.100 gm (Table 2). The observation indicates that, 0.075 gm of catalyst is sufficient to complete the reaction in short time with excellent yield. Further increase in amount of catalyst has no effect on yield and rate of reaction.

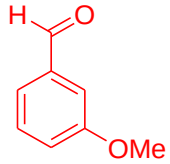
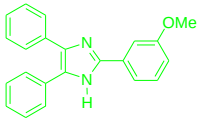
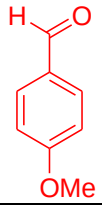
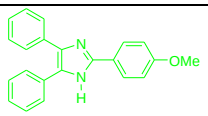
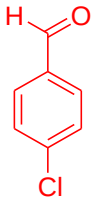
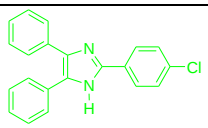
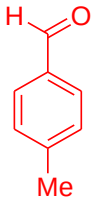
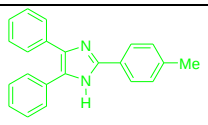
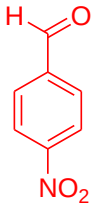
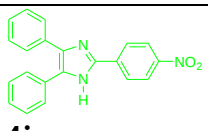
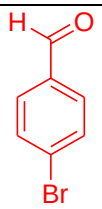
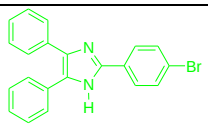
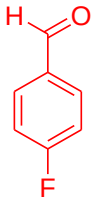
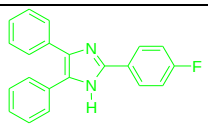
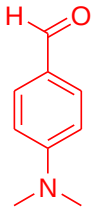
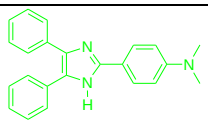
Table 3 Optimization of Time for trisubstituted imidazole reaction

Sr. No	Time (min)	Yield (gm)
1	5	18
2	10	37
3	15	53
4	25	91

Under the optimized condition for exact time determination the model reaction of benzil (1 mmol), 4-methoxy benzaldehyde (1 mmol) and ammonium acetate (3 mmol) under solvent-free condition at 140°C and at constant catalyst amount (0.075 gm). It is observed that 25 min is suitable time for synthesis of trisubstituted imidazole derivatives.

Table 4 Synthesis of 2, 4, 5 Trisubstituted imidazole derivatives

Sr. No	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C)	
					Observed	Reported
1		 **4a**	17	82	268-270	270-271 [xvii]
2		 **4b**	35	91	226-227	225-227[xl]
3		 **4c**	23	88	196-197	195-197[xxix]
4		 **4d**	21	90	232-233	230-231 [xvii]
5		 **4e**	18	89	292-293	290-291 [xvii]

6		 **4f**	43	86	260-262	260-262 [xxxi]
7		 **4g**	25	91	229-230	231-232 [xx]
8		 **4h**	15	93	262-263	260-261 [xviii]
9		 **4i**	29	85	237-238	236-238 [xviii]
10		 **4j**	13	94	239-240	240-242 [xx]
11		 **4k**	29	92	261-262	260-262 [xviii]
12		 **4l**	22	88	232-233	231-233[xxix]
13		 **4m**	35	87	261-262	260-261 [xvii]

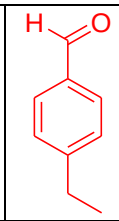
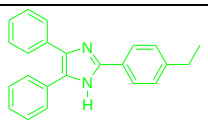
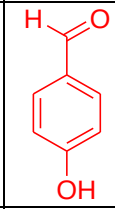
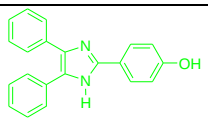
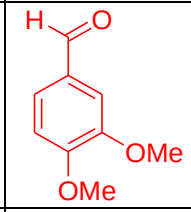
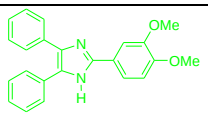
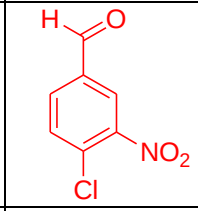
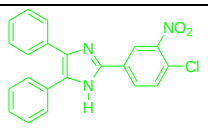
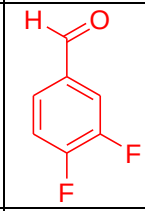
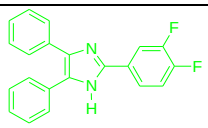
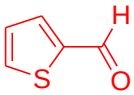
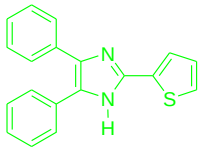
14		 **4n**	33	92	258-260	-
15		 **4o**	27	86	239-241	238-240[xix]
16		 **4p**	30	93	254-255	255-256 [xxxi]
17		 **4q**	43	78	286-290	-
18		 **4r**	42	83	284-290	-
19		 **4s**	45	82	258-260	257-259[xix]

Table 5 Comparison of results with reported method for the synthesis of trisubstituted imidazoles

E Entry	**Catalyst**	**Amount**	**Solvent**	**Temp**	**Time (min)**	**Yield[a]**
1	Cu/C NPs	1 mol %	PEG-200	100°C	90-360	76-93[lvi]
2	Water extract of pomelo (WEP).	100 mg	Solvent-free	rt	360-480	88-98 [lvii]
3	Fe_3O_4@g-C_3N_4	20 mg	EtOH	78 C	120	70-95 [xviii]
4	MCS-GT@Co(II)	5 mg	EtOH	reflux	8-1440	52-99 [lviii]
5	A-MFGO	0.5 gm	EtOH	reflux	120	81-95[lix]
6	Nanosilica-supported Imidazolium Ionic Liquid	0.2 mol %	Solvent-free	120°C	15-100	90-98[lx]

7	$[P_4\text{-VP}]\text{-}Fe_3O_4$	100 mg	Solvent-free	100°C	35-240	79-92 [xxxi]
8	lactic acid	1 mmol,	Solvent-free	160°C	50-180	84-94 [xxxii]
9	$CoFe_2O_4$ MNPs	20 mg	EtOH	reflux	240	85-93 [l]
10	$(CTA)_3PMo$-MMT	50 mg	Solvent-free	100°C	45-120	80-97 [lxi]
11	Fe_3O_4@chitosan nanoparticles	0.05 gm	EtOH	reflux	60-180	90-98 [lxii]
12	$Fe_3O_4@SiO_2$-EP-HEAF	0.02 gm	EtOH	80°C	40–180	75-95 [lxiii]
13	pyridine-2-carboxlic acid	0.5 eq	Solvent-free	150°C	120-180	74-96 [xlii]
14	Cu/C NPs	(1 mol %)	PEG 200 (2 mL).	100°C	90-360	76-93 [lvi]
15	Choline chloride and oxalic acid	(0.5 ml)	Solvent free	110°C	60	85-90 [lxv]
16	Perchloric Polyborate	75 mg	Solvent-free	140°C	13-45	78-94 Present Work

[a]Isolated Yields

EXPERIMENTAL:

All chemicals used in this study were of AR grade and used without further purification. The progress of reaction was monitored by TLC using silica G_{60} F_{254} plates (Merck). The melting points were recorded in open capillary tube and are uncorrected. FT-IR spectrum was recorded on Perkin-Elmer, FT-IR spectrometer. The ^{1}H-NMR was recorded on Bruker Avance 500 MHz NMR spectrometer. Mass spectrum was recorded on Waters Q-ToF Micromass spectrometer.

PREPARATION OF CATALYST:

Dropwise addition of $HClO_4$ (8.605 g) to a conical flask containing polyborate (20.500 g) at very low temperatures (10–15°C) in 80 mL of ether acting as a solvent, followed by magnetic stirring for two hours at room temperature and further reaction content was left for evaporation of ether solvent. Reaction mixture was wash with acetone and dried at room temperature to give perchloric polyborate free flowing powder. Prepared catalyst our previously reported work[lxiv].

GENERAL PROCEDURE FOR SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLE DERIVATIVES:

Perchloric polyborate catalyst (75 mg) was added to a mixture of benzil (1 mmol), substituted aromatic aldehydes (1 mmol), and ammonium acetate (3 mmol) as a source of ammonia. The resulting mixture was heated at 140°C (bath temperature) under solvent-free conditions. After the completion of reaction hot ethanol (6 mL) added in reaction flask to recrystallize compounds and its progress as indicated by TLC (eluent = n-hexane- Ethylacetate, 7: 3). All products were identified by comparison of their physical constant with previous literature and spectroscopic data.

CHARACTERIZATION:

Compound 4h: 2-(4-chlorophenyl)-4, 5-diphenyl-1H-Imidazole

IR (υmax, cm^{-1}): 3430, 3029, 2925, 2852, 1633, 1604, 1484, 1445, 1326, 1127, 1092, 1018, 970, 916, 834, 769, 732, 697, 506 ; ^{1}H NMR (500 MHz, DMSO, δ ppm): 12.75 (s, 1H), 8.11(dd, 2H, j = 9.2 Hz), 7.48 (m, 6H), 7.24 (m, 6H),^{13}C NMR (125 MHz, DMSO, δ ppm): 144.38, 132.69, 129.15, 128.69, 126.78, 126.54,HRMS for $C_{21}H_{15}ClN_2$ (m/z): Calculated $[M+H]^+$ = 330.8102 and observed $[M+H]^+$ = 331.1095.

Compound 4p: 2-(3,4 dimethoxy)-4, 5-diphenyl-1H-Imidazole

IR (υ_{max}, cm^{-1}): 3431, 3012, 2957, 2951, 2837, 2727, 1606, 1493, 1459, 1332, 1258, 1235, 1178, 1142, 1121, 1075, 1025, 998, 921, 866, 809, 767, 697, 635 ; ^{1}H NMR (500 MHz, DMSO, δ ppm): 7.67 (dd, 2H, J = 8.25 Hz), 7.53 (dd, 4H, J = 8.4 Hz), 7.35 (t, 4H, J = 7.75 Hz), 7.27 (t, 2H, J = 7.4 Hz), 7.05 (d, 1H, J =8.35 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 1.78 (s, 1H); ^{1}C NMR (125 MHz, DMSO, δ ppm): 173.45, 148.99, 148.74, 145.67, 133.22, 128.32, 127.67, 126.94, 123.20, 117.88, 111.76, 108.81, 55.51, 55.46: HRMS for $C_{23}H_{20}N_2O_2$ (m/z): $[M+H]^+$ = 356.4171 and observed $[M+H]^+$ = 357.1716 .

Compound 4g: 2-(4-methoxymethoxy)-4, 5-diphenyl-1H-Imidazole:

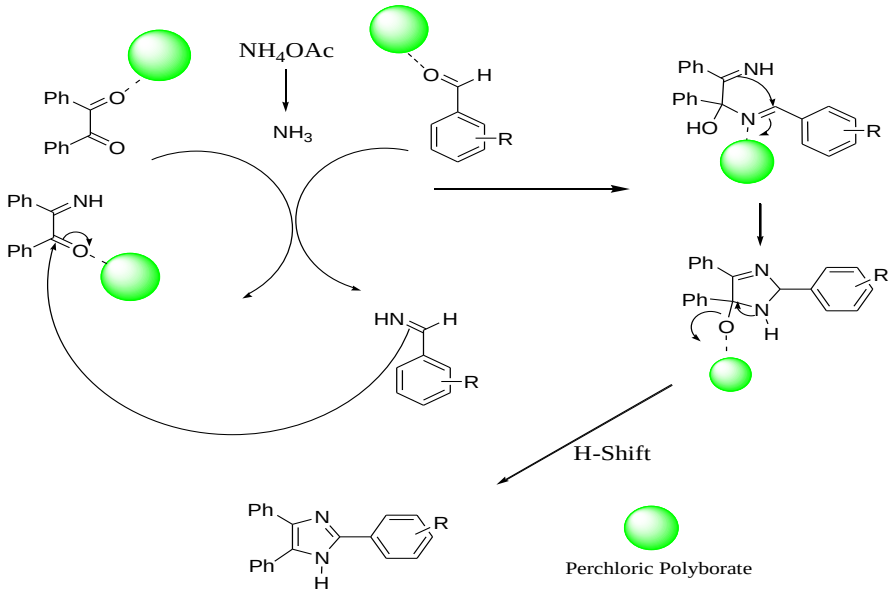
IR (υ_{max}, cm^{-1}):3438, 3061, 2960, 2839, 2050, 1614, 1543, 1494, 1446, 1408, 1387, 1292, 1251, 1178, 1128, 1073, 1031, 970, 914, 833, 768, 738, 697, 611, 515; ^{1}H NMR (500 MHz, DMSO, δ ppm): 12.50 (s, 1H), 8.02 (br, d, 2H, J = 8.8 Hz), 7.49 (br, d, 4H, J = 5.7 Hz), 7.21-7.43 (m, 6H), 7.03 (d, 2H, J = 8.85 Hz), 3.67 (s, 3H); ^{13}C NMR (125 MHz, DMSO, δ ppm): 159.31, 145.52, 136.65, 135.22, 131.13, 128.50, 128.24, 128.14, 128.03, 127.48, 127.11, 126.94, 126.59, 126.28, 123.03, 113.98, 55.09; HRMS for $C_{22}H_{18}N_2O$ (m/z): $[M+H]^+$ = 326.39112 and observed $[M+H]^+$ = 327.1651 .

Compound 4n: 2-(4-ethyl phenyl)-4, 5-diphenyl-1H-Imidazole:

IR (υ_{max}, cm^{-1}): 3427, 3080, 2962, 2930, 2869, 2800, 2634, 1634, 1603, 1492, 1448, 1388, 1321, 1256, 1130, 1071, 1026, 969, 915, 836, 768, 698, 618, 526 ; ^{1}H NMR (500 MHz, DMSO, δ ppm): 12.60 (s, 1H), 8.01 (br, d, 2H, J = 8.2 Hz), 7.47 (d, 4H, J = 5 Hz), 7.21-7.45 (m, 8H), 2.49 (q, 2H, J = 7.6 Hz), 1.20 (t, 3H, J = 7.6 Hz); ^{13}C NMR (125 MHz, DMSO, δ ppm): 145.60, 143.83, 142.02, 137.91, 137.07, 136.86, 135.18, 134.76, 128.50, 128.30, 128.15, 128.04, 127.93, 127.86, 127.56, 127.20, 127.11, 126.97, 126.33, 125.15, 27.88, 15.28; HRMS for $C_{23}H_{20}N_2$ (m/z): $[M+H]^+$ = 324.4183 and observed $[M+H]^+$ = 325.1827 .

REACTION MECHANISM:

Plausible reaction mechanism was proposed for four component synthesis of trisubstituted imidazole as depicted in Scheme 4. The aldehyde and benzil would be activated by the perchloric polyborate catalyst due to its Lewis acid nature. In presence of catalyst the benzil enolises and undergoes Knoevenagel condensation to give intermediate. The activated intermediates react with ammonium acetate to give enamine. The subsequent Michael addition of enamine to intermediate followed by sequential cyclization and dehydration reactions gives trisubstituted imidazoles.



CONCLUSION:

We have developed a simple, efficient and environmentally bengin protocols including three component condensation reaction in which perchloric polyborate was used as an efficient catalyst for synthesis of 2, 4,5-trisubstituted-1*H*-imidazoles via one-pot condensation of benzil, substituted aromatic aldehydes and ammonium acetate. Products have good pharmaceutical and biological importance. The protocol offers good features such as mild reaction condition, low catalyst loading, high yields, ease of catalyst separation and simple workup procedure are the main features of this methodology. This superiority makes the protocol important from the synthetic points of view in biologically active complex drug molecules.

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CONFLICT OF INTEREST:

No potential conflict of interest was reported by the authors.

ABBREVIATIONS:

MCRs = Multicomponent Reactions
NR = No Reaction
SF= Solvent-Free Reactions
FT-IR= Fourier Transform Infrared Spectroscopy
^{1}H NMR = Proton Nuclear Magnetic Resonance Spectroscopy
^{13}C NMR= Carbon Nuclear Magnetic Resonance Spectroscopy

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