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ANHYDROUS $FePO_4$: A GREEN AND COST-EFFECTIVE CATALYST FOR THE ONE-POT THREE COMPONENT SYNTHESIS OF 2, 4, 5-TRIARYLATED IMIDAZOLES

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Abstract – A simple and efficient synthesis of 2,4,5-triarylated imidazoles is achieved by three-component cyclocondensation of benzil and benzoin, aryl aldehyde and ammonium acetate using $FePO_4$ as a catalyst in refluxing ethanol. The key advantages of this process are high yields, cost effectiveness of catalyst, easy work-up, purification of products by non-chromatographic methods and developing of a new derivative of 2,4,5-triarylated imidazole.

INTRODUCTION

Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes [1] such as viz. histidine, histamine and biotin, an active component in several drug molecules [2] and pesticides [3] have received a lot of attention in recent years. Also different substituted imidazoles show a broad range of biological activities such as anti-inflammatory activity,[4] anti-allergic activity,[5] and analgesic activity.[6] In addition, many of the substituted diaryl imidazoles are known as potential inhibitors of the p38 MAP kinase.[7] Among these imidazoles, 2, 4, 5-triphenylimidazoles can be used as light-sensitive materials in photography, fungicides and herbicides, plant growth regulators,[8] and other type of therapeutic agents. Appropriately substituted imidazoles are extensively used as glucagons receptors[9] and CB1 cannabinoid receptor antagonists,[10] modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR),[11] antibacterial,[12] and antitumor[13] agents.

The first synthesis of the imidazole core was reported in 1882 by Radziszewski and Jaap, starting from 1,2-dicarbonyl compounds, aldehydes and ammonia, to obtain 2,4,5-triphenylimidazole.[14] The great biological importance of the imidazole nucleus over the years has raised the development of new and improved methodologies.

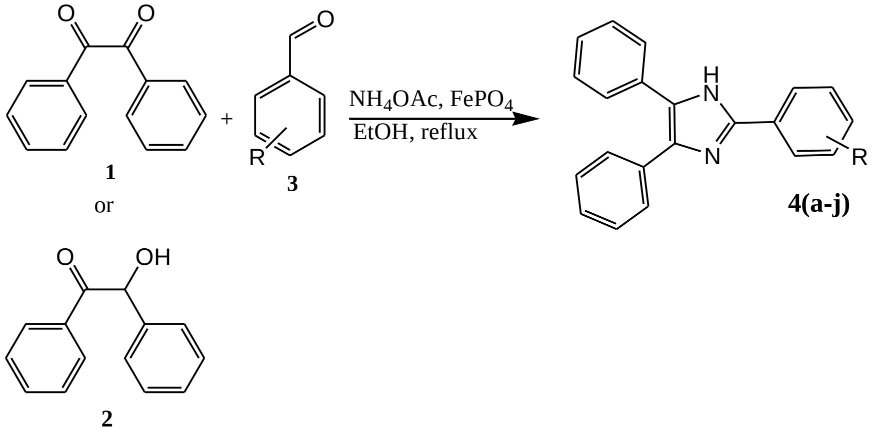
Varying the methods reported to synthesize imidazoles such as hetero-Cope rearrangement,[15] four-component condensation of aryl glyoxals, primary amines, carboxylic acids and isocyanides on Wang resin,[16] reaction of N-(2-oxo)-amides with ammonium trifluroacetate,[17] 1,2-aminoalcohols in the presence of PCl_5,[18] diketones, aldehyde, amine and ammonium acetate in phosphoric acid,[19] in acetic acid,[20] organo catalyst in acetic acid[21] as well as H_2SO_4[22] and DMSO.[23]

Also several micro-wave (MW) assisted syntheses of imidazoles from 1, 2-diketones and aldehydes in the presence of a variety of catalysts have been reported. These include MW/silica-gel,[24] MW/Al_2O_3,[25] MW/acetic acid,[26] in DMF. The condensation of α-hydroxyl ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in the presence of MW.[27]

Recently, the synthesis of these imidazoles has been catalyzed by silica gel or Zeolite HY,[28] molecular iodine,[29] $H_3PW_{12}O_{40}$, [30] $Yb(OTf)_3$,[31] $NdCl_3$,[32] $LaCl_3$,[33] $FeCl_3$,[34] $AlCl_3$,[35] Al_2O_3,[36] $NiCl_2$,[37] [HBim]BF_4,[38] $InCl_3 \cdot 3H_2O$,[39] ionic liquid,[40] silica sulfuric acid,[41] ytterbium perfluorooctanesulfonate ($Yb(OPf)_3$),[42] $Zr(acac)_4$,[43] and tetrabutylammonium bromide.[44]

Although these methods possess a lot of alternative, the reactions suffer from low yields, longer reaction times, use of expensive reagents, use of toxic solvents and agents associated with a mixture of products and lack of generality, thus they were not suitable for, or were not applied for, the synthesis of structurally diverse imidazoles**.**

In addition to cases mentioned above, $FePO_4$ is cheap, safe, and available reagent[45] that has also been employed for the selective oxidation of CH_4 to CH_3OH[46] and benzene to phenol[47] and one-pot synthesis of dihydropyrimidinones and thiones[48] as a catalyst. Therefore, in connection with our research[49] for the development of simple and efficient methods for the synthesis of various heterocyclic compounds herein, we present iron (III) phosphate as a green, reusable, recyclable, safe-environmentally, inexpensive and commercially catalyst for the synthesis of 2,4,5-triaryl-1*H*-imidazoles (Scheme 1).



Scheme 1. Synthesis of 2, 4, 5-triarylimidazoles using $FePO_4$

RESULTS AND DISCUSSION

The reaction conditions (solvent, reaction time, and catalytic amount of catalyst) were studied to standardize this procedure. The results on the synthesis of 2,4,5-triphenyl-1*H*-imidazole from the reaction of benzil, benzaldehyde, ammonium acetate, water and ethanol using $FePO_4$ are summerized in Table 1. Of solvents including ethanol, water, and ethanol/water, ethanol proved to be the best in terms of yield. Thus in present study has been used only ethanol, which is relatively benign organic solvent. We found that, the heterocyclization reaction is facilitated by increasing the temperature, so the reaction proceeded in ethanol under reflux condition to give a high yield at a relative short reaction time.

Table 1. Effect of varying the solvent and the amounts of $FePO_4$ on the yields and reaction times of synthesis of 2,4,5-triphenyl-1*H*-imidazole using 1.0 mmol each of benzil and benzaldehyde under reflux conditions 4a

Solvent	$FePO_4$ (mol %)	Time (h)	Yield %
H_2O	15	24	10
EtOH- H_2O (1:1)	15	5	75
EtOH- H_2O (3:1)	15	4	80
EtOH	15	2	94
EtOH	10	2	94
EtOH	7	3	85
EtOH	5	4	80

The amount of NH_4OAc required for reaction and to increase the yield of 2,4,5-triphenyl-1*H*-imidazole was investigated, and the results are summarized in Table 2. As shown, the optimum amount of NH_4OAc was 5 mmol in the presence of 1 mmol each of benzaldehyde and benzil.

Table 2. Effect of varying the amounts of NH_4OAc on the yields of 2,4,5-triphenyl-1*H*-imidazole

Solvent	**NH_4OAc (mmol)**	**Time (h)**	**Yield %**
EtOH	1.2	48	70
EtOH	2.5	48	70
EtOH	4.0	10	80
EtOH	5.0	2.0	94

To illustrate the need of catalyst, $FePO_4$, for this reaction, experiments were conducted in which the model reaction of was studied in the absence of catalyst. The reaction was not completed even after 24 h. Undoubtedly, the catalyst is an efficient component of the reaction. The amount of the catalyst required for the reaction and to increase the yield of 2,4,5-triphenyl-1*H*-imidazole was investigated, and the results are summarized in Table 1. Results clearly indicate that 10 mol% of $FePO_4$ is sufficient to catalyze the cyclocondensation reaction.

In order to show the merits of the present work, the variety of aldehydes with electron-donating and electron-withdrawing groups on the aromatic ring, benzil, benzoin, ammonium acetate and $FePO_4$ in ethanol were subjected for synthesis of 2,4,5-triarylated-1*H*-imidazole. We found that for aldehydes bearing either electron-releasing or electron withdrawing substituents in the ortho, meta or para positions, the reaction proceeded very efficiently in all cases (Table 3).

1, 2-diketones (like benzil) are usually prepared from the α-hydroxy ketones (like benzoin) catalyzed by various oxidants. Some of these catalysts are toxic, costly and also required the tedious experimental procedures.[50] Aimed to evaluate direct oxidation condensation reaction, the synthesis of 2,4,5-triphenyl-1*H*-imidazole was studied using benzoin (Table 3: entry 1). Surprisingly, using the similar reaction conditions, 2,4,5-triphenyl-1*H*-imidazole was isolated in 92% yield. Encouraged by this result, we extended the methodology for synthesis of various 2,4,5-triaryl-1*H*-imidazoles using benzoin and various aromatic aldehydes. The yields obtained were in the range of 72 to 95%.

The overall greenness of this reaction was high as minimum amount of environmentally benign ethanol and $FePO_4$ were used during the course of reaction. Moreover, it is important to note that in all cases, after completion of the reaction $FePO_4$ filtrated off and reused for another run (Table 4). Imidazoles were also precipitated on dilution of the reaction mixture with water and were isolated by a simple filtration. The dried product that obtained showed a single spot on TLC and was pure enough for all practical purposes. The other advantages of this research are synthesis of (E)-4,5-diphenyl-2-styryl-1*H*-imidazole and 2-(3,5-dichlorophenyl)-4,5-diphenyl-1*H*-imidazole for first time as a new imidazole derivatives (Table 3: entries 4, 6). We are willing to survey their biological properties in future.

A probable mechanism for the synthesis may be postulated as shown below (Scheme 2). $FePO_4$ is Lewis acid because of the hard character of its metal cation, so that it can activate the carbonyl group (C=O) to decrease the energy of transition state. It is highly probable that the carboxyl groups of benzil **1** and aldehydes **3** have to be activated which occurs when the carbonyl oxygen is coordinated by $FePO_4$. Then nucleophilic attack of the nitrogen of ammonia obtained from NH_4OAc on the activated carbonyl group, resulted in formation of aryl aldimine **6** and α-imino ketone **5**, and it followed by the nucleophilic attack of the in situ generated imine **6** to carbonyl of aryl aldimine **3**, giving the intermediate **7**. Their subsequent intramolecular interaction leads to cyclization and eventually to the formation of intermediate **8**, which dehydrates to the trisubstituted imidazoles **4**.

CONCLUSION

In summary, this manuscript describes a simple, convenient, green, easy and efficient method to prepare a variety of triaryl-substituted imidazoles in the presence of catalytic amount of $FePO_4$. The catalytic activity of $FePO_4$ is remarkable and the use of low cost, commercially available $FePO_4$ as catalyst for the synthesis of triaryl imidazoles in excellent yields is also significant under the aspect of environmentally benign processes. The advantages, such as shorter reaction times, product yields, the easy procedure to carry out the reaction makes the inexpensive and commercially available $FePO_4$ as a powerful catalyst for the synthesis of imidazoles.

Table 3. Synthesis 2, 4, 5-triaryl-1*H*-imidazoles using benzil or benzoin, ammonium acetate, aromatic and aliphatic aldehydes, and 10 mol% $FePO_4$

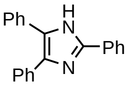
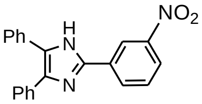
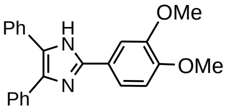
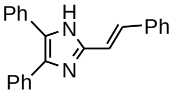
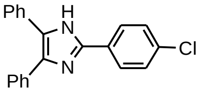
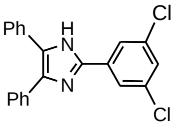
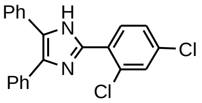
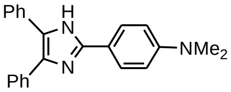
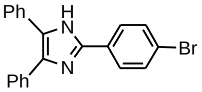
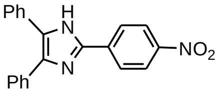
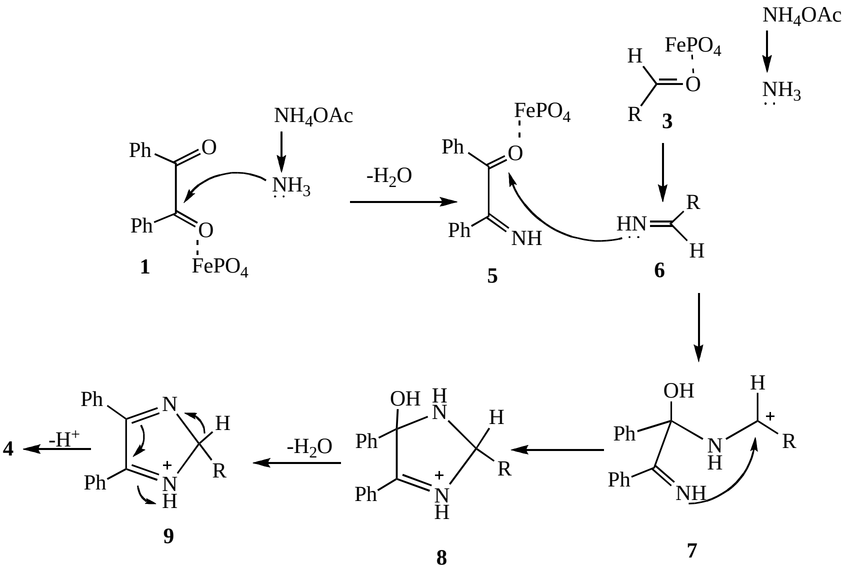
Entry	ArCHO	Product	Time (h)		Yield (%)		Mp (˚C)	
			benzil 1	benzoin 2	benzyl 1	benzoin 2	Found	Reported
1	C_6H_5CHO **3a**	 **4a**	2.0	2.5	94	92	274-275	275[15]
2	3-nitro-C_6H_4CHO **3b**	 **4b**	3.0	3.5	96	95	316-317	314-315[15]
3	3,4-diMeO-C_6H_3CHO **3c**	 **4c**	2.5	3.0	93	90	216-217	220-221[30]
4	*trans*-$C_6H_5CH=CHCHO$ **3d**	 **4d**	2	2.5	95	93	272-273	---
5	4-Cl-C_6H_4CHO **3e**	 **4e**	4.5	5.0	85	81	259-260	261-263[15]
6	3,5-diCl-C_6H_4CHO **3f**	 **4f**	4.0	4.5	92	90	172-173	---
7	2,4-diCl-C_6H_4CHO **3g**	 **4g**	6.0	6.5	74	72	177-178	176-177[51]
8	4-*N,N*-diMe-C_6H_4CHO **3h**	 **4h**	3.0	3.5	88	85	249-250	257-258[30]
9	4-Br-C_6H_4CHO **3i**	 **4i**	3.0	3.5	87	85	237-238	248-249[52]
10	4-nitro-C_6H_4CHO **3j**	 **4j**	3.5	4.0	94	91	182-183	196-197[15]

Table 4. Recycling and reusing of the catalyst for the synthesis of 2-(4-chlorophenyl)- 4,5-diphenyl-1*H*-imidazole has been shown

Entry	**Aldehyde**	**Yield% [Time(h)]**	
		Benzil	**Benzoin**
1	4-chlorobenzaldehyde	85[4.5]	81[5.0]
2	"	83[4.5]	80[5.0]
3	"	83[4.5]	80[5.0]



Scheme 2. Plausible mechanism for the synthesis of 2,4,5-triarylimidazoles using $FePO_4$

EXPERIMENTAL

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm^{-1}. The products were characterized by IR, ^{1}HNMR. All melting points compared satisfactorily with those reported in the literature.[15, 30, 51, 52]

Preparation of 2, 4, 5-triaryl-imidazoles: typical procedure

A mixture of benzaldehyde (1.0 mmol), benzil/benzoin-air exposure (1.0 mmol) and NH_4OAc (5.0 mmol), as ammonia source, and $FePO_4$ (10 mol %) stirred refluxing in ethanol (4.0 mL) and air exposure. The progress of the reaction was monitored by TLC and the spot were detected either UV light or by placing in iodine chamber. After completion of the reaction, the mixture was filtered, removed catalyst and the filtrate was cooled to room temperature and the corresponding pure product obtained in 94% yield.

Spectral and analytical data for new compounds

(*E*)-4, 5-Diphenyl-2-styryl-1*H*-imidazole 4d, IR (cm^{-1}, KBr): 3393(N-H), 3027(C-H), 1601(C=C), 1580 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz, δppm): 9.38(s, NH), 7.90(d, J=7.45Hz, 1H), 7.26-7.66(m,15 H, Ph), 7.37(d, J=14.70 Hz, 1H); MS (EI, 70 eV): m/z = 322.147 (100.0%), 323.150 (24.9%), 324.154 (3.0%); Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.21; H, 5.33; N, 8.31.

2-(3,5-Dichlorophenyl)-4,5-diphenyl-1*H*-imidazole 4f, IR (cm^{-1}, KBr): 3436(N-H), 3060(C-H), 1600(C=C), 1591(C=N) cm^{-1}. ^{1}H NMR($CDCl_3$, 500MHz, δppm): 10.18(s, NH), 7.17-7.34(m,3H,Ph), 7.37-8.42(m, 10H, Ph); MS (EI, 70 eV): m/z = 364.053 (100.0%), 366.050 (63.9%), 365.057 (22.7%), 367.054 (14.5%), 368.048 (10.2%), 366.060 (2.5%), 369.051 (2.3%), 368.057 (1.6%); Anal. Calcd for

$C_{21}H_{14}Cl_2N_2$: C, 69.05; H, 3.86; Cl, 19.41; N, 7.67. Found: C, 68.83; H, 3.59; Cl, 19.06; N, 7.23.

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