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SYNTHESIS AND CHARACTERIZATION OF NOVEL SERIES OF THE IMIDAZOLES UNDER SOLVENT FREE CONDITIONS BY USING SODIUM DIHYDROGEN PHOSPHATE

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ABSTRACT:2,4,5-triphenylimidazoles/1-(2-Methyl)-3-(2-hydroxyphenyl)imidazo[1,5-a]pyridine could be obtained in excellent yields by the one-pot three-component condensation of benzil/2-acetyl pyridine, aldehyde and ammonium acetate in the presence of catalytic amount of the inexpensive, readily available NaH_2PO_4 under solvent-free condition. The mixture was ground together in a mortar with a pestle at room temperature for short reaction time and easy operation under solvent free condition.

Keywords: 2, 4, 5-triphenyl imidazole/1-(2-Methyl)-3-(2-hydroxyphenyl)imidazo[1,5-a]pyridine; aldehydes; NaH_2PO_4; ammonium acetate.

INTRODUCTION

To design and conduct chemical reaction with "green" experimental protocol is an enormous challenge that chemists have to confront to improve the quality of the environment for present and future generations. Target areas for achieving this goal are the exploration of alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste, and elimination of the use of conventional organic solvents, wherever possible. Traditional chemical syntheses or transformations generally require volatile and often hazardous organic solvents as reaction media to facilitate mass and heat transfer, and to isolate and purify desired product from reaction mixtures. Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. Organic solvent are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store. In recent years, solid-state organic reactions have caused great interest. They have many advantages such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions and benefit industry as well as the environment[1]. Many articles about solid-state reactions with grinding have been reported, such as the Grignard reaction[2], aldol condensations[3], and other reactions[4].Imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds such as antiulcerative agent cimetidine[5] the proton pump inhibitor omeprazole[6] and the benzodiazepine antagonist flumazenil[7] are imidazole derivatives. In addition, the substituted imidazole ring systems are substantially used in ionic liquids[8] that have been given a new approach to 'Green Chemistry'. Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2-dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenyl imidazoles[9,10]. Also, Grimmett et.al. proposed the synthesis of the imidazole using nitriles and esters[11]. Recently, there are several methods reported in the literature for the synthesis of 2, 4, 5-triphenylimidazoles using zeolite HY/silica gel[12], $ZrCl_4$ [13], $NiCl_2{\cdot}6H_2O$[14], ionic liquid[15], iodine[16], sodium bisulfite[17]. However, these methods require prolonged reaction time and exotic reaction condition.

Thus, the development of a new method for the synthesis of imidazoles derivatives would be highly desirable. In recent years, NaH_2PO_4 has gained special attention as a catalyst in organic synthesis because many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness, eco-friendly nature, readily available and high reactivity.

EXPERIMENTAL

The melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on jasco FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on 80 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (PPM) relative to tetramethylsilane (Me_4Si) as an internal standard. Mass spectra were recorded on micromass Quattro II using electrospray ionization technique.

Synthesis of 2, 4, 5-triphenyl imidazole/1-(2-Methyl)-3-(2-hydroxyphenyl) imidazo [1,5-a]pyridine (3)

A mixture of benzaldehyde (1mmol), benzil/2-acetyl pyridine, (1 mmol), NH_4OAC (2.5 mmol) and NaH_2PO_4 (10 mmol %) were ground together in a mortar with a pestle at room temperature for appropriate time (Table 2). After completion of reaction confirmed by TLC, the mixture was treated with water to furnish the crude products. The crude was further purified by column chromatography by using methanol: benzene (25:75) eluent and recrystallised from methanol.

2,4,5-Triphenyl-1*H*-imidazole (3a): mp.270 ^{0}C (Lit[18] 272-273^{0}C).(Found C, 85.02, H,5.1, N,9.12%. $C_{21}H_{16}N2$ requires C, 85.11, H, 5.44, N, 9.45%) ν_{max};(KBr)/ cm^{-1} 3434, 2993, 2470, 1638, 1216. ^{1}H NMR ($CDCl_3$/DMSO-d_6)δ_H 12.61 (1H,br s), 7.42-8.12 (15H,m); ^{13}C NMR ($CDCl_3$/DMSO-d_6):δ_C 136.5, 129.1, 128.5, 127.2, 122.1

2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (3b): mp 226 ^{0}C; (Lit.[18] 228 ^{0}C). (Found: C, 80.68, H, 5.23, N, 8.42%. $C_{22}H_{18}N_2O$ requires C, 80.96, H, 5.56, N, 8.58 %)ν_{max} ; (KBr)/cm^{-1} 3428, 2893, 2465, 1636, 1216; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ_H 3.85 (s, 3H), 12.52 (1H, br s), 8.02-8.05 (2H, d), 7.25-7.59 (10H, m), 6.93-6.96 (2H, d), 3.85 (3H, s); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ_C 159.1, 145.7, 132.8, 127.6, 126.5, 126.3, 122.7, 113.2, 54.6

2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-3-methoxy phenol (3c): mp. 168 ^{0}C (Lit.[18]) (Found: C, 77.05, H, 5.18, N, 8.42%. $C_{22}H_{18}N_2O_2$ requires C, 77.17, H, 5.30, N, 8.18%) ν_{max} ; (KBr)/cm^{-1} 3611, 3412, 2923, 1652, 1253; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ_H 3.86 (s, 3H), 6.82-6.85 (m, 3H), 7.29-7.32 (m, 5H), 7.53-7.55 (m, 5H), 12.5 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ_C 126.3, 126.7, 127.3, 127.4, 129.8, 147.3, 146.1, 145.3, 129.8, 127.4, 127.3, 126.7, 126.3, 117.1, 155.6, 112.1, 110.9, 54.7

2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-6-methoxy phenol (3d): mp. 168 ^{0}C; IR (cm^{-1}) 1253, 1654, 2925, 3412, 3610; ^{1}H NMR ($CDCl_3$/DMSO-d_6,200 MHz) δ 3.86 (s, 3H), 6.82-6.85 (m, 3H), 7.29-7.32 (m, 5H), 7.53-7.55 (m, 5H), 12.4 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 54.3, 110.9, 112.1, 155.6, 117.1, 126.3, 126.6, 127.3, 127.4, 129.8, 145.1, 146.1, 147.3; $C_{22}H_{18}N_2O_2$(342): Anal. Calcd for C, 77.17, H, 5.30, N, 8.18; Found: C, 77.18, H, 5.18, N, 8.02.

2-(4, 5-Diphenyl-1*H*-imidazol-2-yl)-phenol (3e): mp. 205 ^{0}C; IR (cm^{-1}) 1216, 1636, 2465, 2998, 3432, 3596; ^{1}H NMR ($CDCl_3$/DMSO-d_6,200 MHz) δ 6.87-6.95 (d, *J* = 7.5Hz, 2H), 6.96-7.01 (d, *J* = 8.06 Hz, 1H), 7.17-7.23 (m, 10H), 12.74 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 112.7, 116.4, 118.1, 124.8, 126.8 127.4, 127.8, 129.1, 145.7, 156.6; $C_{21}H_{16}N_2O$ (312): Anal. Calcd for C, 80.75, H, 5.16, N, 8.97; Found: C, 80.62, H, 5.08, N, 8.85.

4-(4, 5-Diphenyl-1*H*-imidazol-2-yl)-phenol (3f): mp. 231 ^{0}C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432, 3596; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.93-6.97 (d, *J* = 8Hz, 2H), 7.52-7.87 (m, 10H), 7.88-7.92 (d, *J* = 8.5 Hz, 2H), 12.58 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 113.7, 119.9, 125.1, 125.3, 126.1, 126.5, 144.7, 159.2; $C_{21}H_{16}N_2O$ (312): Anal. Calcd for C, 80.75, H, 5.08, N, 8.97; Found: C, 80.68, H, 5.05, N, 8.90.

2-(4-Methylphenyl)-4, 5-diphenyl-1*H*-imidazole (3g) mp.158-161 ^{0}C; IR (cm^{-1}) 1215, 1453, 1486, 1496, 1601, 2926; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.30 (s, 3H), 7.41-7.51 (d, 10H), 7.29-8.52 (d, 4H), 13.58 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 48.8, 126.5, 127.1, 128.3, 128.8, 129.5, 130.7, 134.4, 138.2, 147.3.

2-(3-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole (3h) mp. 198-200 ^{0}C; IR (cm^{-1}) 1446.3, 1533.8, 1540.7, 1602.6, 3058; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 13.11 (s, 1H), 8.98 (s, 1H), 8.53 (d, *J* = 9 Hz, 1H), 8.22 (d, *J* = 9 Hz, 1H), 7.76 (t, 1H), 7.25-7.5 (m, 10H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 122.8, 123.9, 127.5, 127.6, 128.7, 129.2, 129.3, 130.1, 131.5, 133.6, 138.2, 148.4, 177.1.

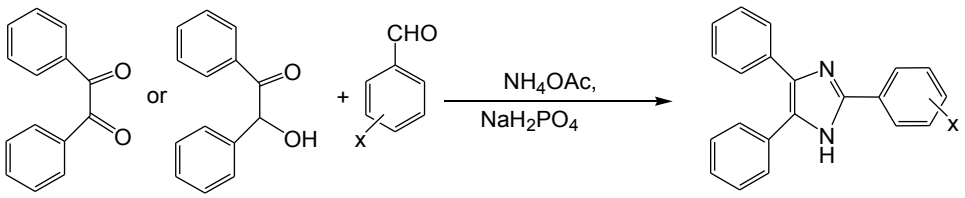
2-(4-Dimethylaminophenyl)-4,5-diphenyl-1*H*-imidazole (3i): mp. 237-240 0C; IR (cm-1) 1445.7, 1508, 1551, 1661, 2919.1, 3057.8; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.98 (s, 6H), 6.78-7.92 (m, 14H), 13.56 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 112, 121.3, 126.9, 127.1, 127.3, 127.8, 127.9, 128.2, 128.3, 129.4, 129.5, 134.5, 145.1, 150.1, 155.3.

1-(2-Methyl)-3-(2-hydroxyphenyl)imidazo[1,5-a]pyridine (3a): mp 150 ^{0}C (Lit.[19] 149-151 ^{0}C). ^{1}H NMR ($CDCl_3$, 200 Mz):δ =7.89 (d,*J* = 8.5 Hz, 1 H), 7.42-7.38 (m, 2 H), 7.08 (m, 2 H), 6.81 (m, 2 H), 6.63 (m, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 155.0, 143.1, 136.0, 131.0, 129.2, 128.0, 126.2, 123.4, 122.0, 119.4, 116.0, 17.0; LC-MS: m/z = 225(M^+); Anal. Calcd for $C_{14}H_{12}N_2O$ (224.2); C, 74.98; H, 5.39; N, 12.49: Found: C, 74.84; H, 5.27; N, 12.38.

1-(2-Phenyl)-3-(2-aminophenyl)imidazo[1,5-a]pyridine (3b): mp 148 ^{0}C (Lit.[19]146-147 ^{0}C); ^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.02 (d,*J* = 8.0 Hz, 2H), 7.48 (m, 1H), 7.36-7.30 (m, 3H), 7.16 (m, 1H), 7.03 (m, 1H), 6.59-6.43, (m, 2H), 6.12 (m, 1H), 5.78 (m, 1H), 4.20 (br s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 145.0, 143.4, 133.5, 130.0, 129.1, 127.7, 122.0, 119.8, 116.3, 110.0; LS-MS: m/z = 286 (M^+). Anal. Calcd for $C_{26}H_{29}N_3O$ (399.53); C, 78.16; H, 7.32; N, 10.52, Found: C, 78.04; H, 7.10; N, 10.20

RESULT AND DISCUSSION

As a part of our ongoing investigation in developing a versatile and efficient method for synthesis of heterocyclic compounds[18], we report here an efficient synthetic method for the synthesis of 2, 4, 5-triphenyl imidazoles from benzil/2-acetyl pyridine, aldehyde and ammonium acetate in the presence of NaH_2PO_4 (Scheme1).

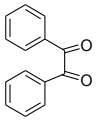
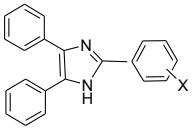
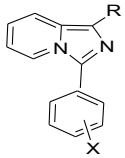


(3a-o)

Scheme 1

Reaction were carried out simply by mixing benzil with an aldehyde and ammonium acetate in the presence of a catalytic amount (15 mmol%) of NaH_2PO_4 under solvent-free condition summarized in Table 2. The mixture was ground together in a mortar with a pestle at room temperature for short reaction time, and then purified by column chromatography, substituted imidazole derivatives were obtained in excellent yields. Accordingly, (10 mmol%) was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher molar ratios of NaH_2PO_4 were used. However , no product formation was observed in absence of NaH_2PO_4.

Table 1. NaH_2PO_4–Catalyzed synthesis of 2, 4, 5-triphenyl imidazole/(2-Methyl)-3-(2-hydroxyphenyl)imidazo[1,5-a]pyridine.

Entry	Ketones**(1)**	Aldehydes **(2)**	Products **(3)**	Yield[a,b] (%)
1				
		a. X = H		93
		b. X = 2-OMe		91
		c. X = 3-OMe, 4-OH		90
		d. X = 3-OMe, 2-OH		90
		e. X = 2-OH		92
		f. X = 4-OH		91
		g. X = 4-Me		93
		h. X = 3-NO_2		92
		i. X = 4-NMe_2		94
		j. X = 4-Cl		92
		k. X = 2-NO_2		91
		l. X = 4-NO_2		92
		m.X = 4-CN		93
		n. X = 2-Cl		91
		o. X = 2,4,6-OMe		90
	 R= Me, Ph			
		a. X = 2-OH		91
		b. X = 2-NH_2		93

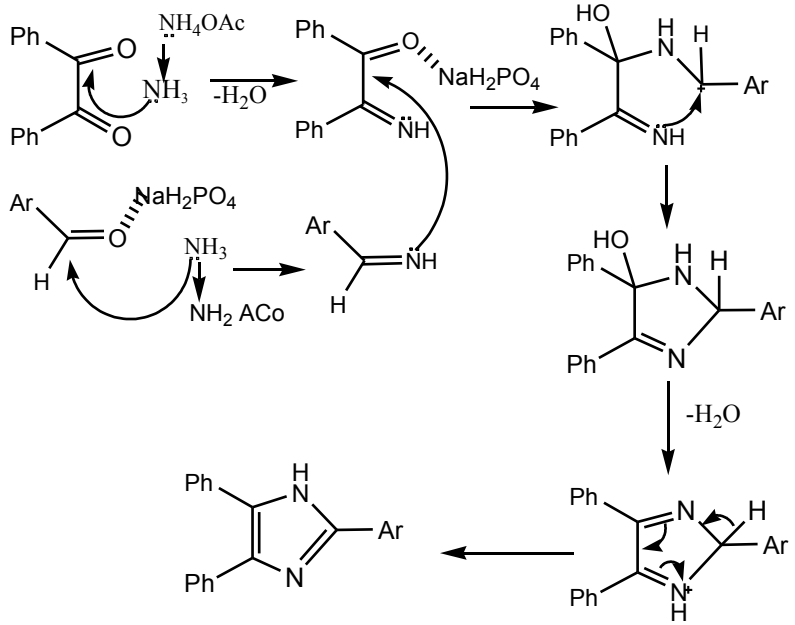
[a]Yield of isolated pure products. [b]Products were characterized by IR, NMR, Mass elemental analysis and comparison with authentic sample[18-21].

Table 2. Catalytic evolution for synthesis of **3** a. X=H under solvent free conditions.

Entry	Time (min)	Yield [a] (%)	NaH_2PO_4 (mmol%)
1	80	00	No
2	50	Traces	1
3	20	20	2
4	15	85	5
5	07	93	10
6	07	93	15

[a]Isolated yield after column chromatography.

By getting this result, we have extended this protocol to a variety of aldehydes and ketones summarized in Table 1. This protocol is rapid and efficient for the preparation of several imidazoles from both electrons efficient as well as electron deficient aromatic aldehydes. Electron-withdrawing groups enhance the rate of the reaction as compare to the electron-donating group. Aliphatic aldehyde and ketones (e.g. acetaldehyde, acetone) were also used as starting carbonyl compounds for the same reaction. No product formation takes place in this reaction by grinding the reagents for more than 30 minutes. The phenyl groups substituted with different groups did not show any effect on the formation of imidazoles. The *ortho* and *para* substituents activate the aromatic ring of aldehydes and increase the rate of the reaction. While *meta* substitution requires somewhat greater time as compared to the *o/p* substituents. Heteroaromatic ketones reacted fast and gave excellent yields of desired imidazoles. A nearly stiochiometric amount of ammonium acetate was used in the course of the reaction, whereas previously a many-fold excess of ammonium acetate was required. This is an additional advantage of the novel methodology. The possible mechanism of this reaction (Scheme 2).



Scheme 2

The acidic nature of molecular NaH_2PO_4 makes it capable of binding with the carbonyl oxygen of aromatic aldehyde increasing the reactivity of the parent carbonyl compound and facilitates the formation of imines intermediate I. Further catalyst NaH_2PO_4 condenses with the carbonyl oxygens of the ketone, which on dehydration afford the intermediate II. Intermediates I and II combine for the formation of intermediate III, which on dehydration and further cyclisation gives 2, 4, 5-triphenyl imidazole/1-(2-Methyl)-3-(2-hydroxyphenyl)imidazo[1,5-a]pyridine **(3)** in 90-93% yield (Scheme 2).

Conclusion

In conclusion, we have developed an efficient and convenient method for the synthesis of imidazole derivatives using cheap and readily available NaH_2PO_4 as a catalyst. The notable merits offered by this methodology are solvent free reaction condtions, simple procedure, cleaner reactions, short reaction time and excellent yield of products.

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