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Ceric ammonium nitrate catalyzed efficient one-pot synthesis of 2, 4, 5-triaryl imidazoles

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ABSTRACT

An efficient and rapid one-pot synthesis of 2, 4, 5-triaryl imidazole is carried out at 75^{o}C using aromatic aldehyde, benzil or benzoin in the presence of catalytic amount of ceric ammonium nitrate. Excellent yield in short reaction time is characterized by simple work up procedure efficient recovery.

Keywords: ceric ammonium nitrate CAN, 2, 4, 5-triaryl imidazole, aromatic aldehyde, benzil, benzoin.

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INTRODUCTION

The imidazole ring system is of particular interest as it is a component of histidine that produces histamine in metabolic process [1]. The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals which are present in many protein active sites. Triaryl imidazoles are used as a photosensitive material in photography [2a]. In addition they are of interest because of their herbicidal [2b], analgesic [3], fungicidal [4], anti-inflammatory [5] and antithrombotic activities [6]. Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazole to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic Carbenes (NHC) [7], imidazoles also have COX-2 inhibitory activity [8].

Generally triaryl imidazoles are prepared by hetro-cope rearrangement [9]or by reaction of glyoxal, formaldehyde and ammonia [10-11]. Previous studies suggested the use of Zn-Al_2O_3 [12], and PCl_5[1] [13]diketones, aldehyde and ammonium acetate in phosphoric acid [14] as well as in H_2SO_4 [15] and DMSO [16] . Micro wave assisted synthesis of imidazoles from 1, 2-diketones in the presence of catalyst such as silica-gel [17], silica-gel/HY [18], MW/Al_2O_3 [19], DMF [20] and MW/acetic acid [21].

Reported methods have one or the other limitations such as harsh reaction conditions, poor yields prolonged time period, use of hazardous and expensive catalysts and polar solvents. Recently ceric ammonium nitrate (CAN) received considerable attention as an inexpensive, nontoxic, readily available catalyst for various transformations, affording the corresponding products in excellent yield with high selectivity, in the proposed work we have synthesized trisubstituted imidazoles from benzil or benzoin with aldehyde at 75^{o}C in the presence catalytic amount of CAN **scheme1** During the course of our studies toward the development of new routs to the synthesis of biologically active heterocycles [22].

RESULT AND DISCUSSION

In continuation to our endeavor to develop the biologically active compounds of substituted imidazole derivatives, we have developed the methodology for the synthesis of 2, 4, 5 trisubstituted imidazoles using neat reaction condition . The synthesis of trisubstituted imidazole by aromatic aldehyde, benzil or benzoin and ammonium acetate in presence of ionic liquid [Hbim]BF_4 [23] is a well established procedure [23]. However, ionic liquid is economically expensive not available easily. When benzyl or benzoin(1a or 1b) and aromatic aldehyde (2a-2h) were treated with a catalytic amount of CAN in acetonitrile for 2-6 hrs, then triarylsubstituted imidazole (3a-3p) were obtained in moderate to good yields **Table 2** .

To examine the catalytic activity of CAN, we explored a modification of the reaction of (1a) or (1b) and aromatic aldehyde in acetonitrile first without CAN then 5mol%, 10mol%, 20mol% and 25mol% amount of CAN. The results are shown in **Table1** page(10).

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According to observations in **Table1** (5mol%) of CAN was enough and efficient, as 90 %, 91% yield (entry 2) for both (1a), (1b) respectively an excessive amount of the catalyst was check for the same reaction condition it is found that at the same reaction time, % yield did not increase. **Table 1** entry (3-5). In the absence of CAN, no reaction was found **Table1**, entry (1). To investigate the real catalyst species CAN, the experiment using $CeSO_4$ 20 mol% in place of CAN has been tried.

The product was obtained in both 1a,1b with yield of 60%, 58% at 75^{o}C **Table 1** entry 6 hence CAN should be the real catalyst species because of its Lewis acidity. Ammonium acetate is a solid source of ammonia which can be conveniently generated in situ through the dissociation of ammonium acetate. Usually, the amount of ammonium acetate used is loosely controlled. A large excess is often used for two reasons one is that it is water soluble and excess amount can be easily removed during a work up and secondly it is a neutral salt and not a significant active species other than as an ammonia source.

According to the literature survey it was reported that Balalai et.al [18] and Qing Xiang Guo [24], synthesized 2, 4, 5 trisubstituted imidazole by using benzoin (1b), zeolite HY and Sio_2 respectively in microwave irradiation in our methodology we were reported the formation of imidazole by using directly benzoin(1b) with the same reaction condition **scheme 1**. The benzoin (1b) reflux with acetic acid and the product was not found even after 24 hrs. When we used CAN a powerful oxidizing reagent scheme **1** we found very good results summarized in **Table 2**.

The CAN has promoted this heterocyclization reaction by virtue of its inherent bronsted acidity which makes it capable of bonding with the carbonyl oxygen increasing the relativities of the parent carbonyl compounds. The CAN promotes the splitting of ammonia required for the initial condensation.

For the postulated mechanism starting from 1, 2-diketone **scheme 2.** The CAN may facilitate the formation of a imine intermediate (4), which under Bronsted acid catalysis of the CAN condenses with the carbonyl carbons of the 1, 2-diketone followed by dehydration to afford the intermediate (5). Intermidiate (4) and (5) combine for the formation of intermediate (6), which on dehydration and further cyclization gives 2, 4, 5 – triaryl substituted imidazole (7).

RESULTS AND CONCLUSION

In conclusion, we have developed an efficient, convenient and one-pot protocol for the synthesis of biologically potent 2, 4, 5-triaryl imidazoles via the condensation of aromatic aldehyde and benzil or benzoin with ammonium acetate using ceric ammonium nitrate. The process gives rise to excellent isolated yield of triaryl imidazole. The study of antimicrobial activity is under progress.

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EXPERIMENTAL

All reported yields are isolated yields. Melting points are uncorrected. and were recorded by open capillary. Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer in (KBr). ^{1}H NMR spectra were recorded on a Bruker AC-200 (MHz) spectro-meterin $CDCl_3$/DMSO-d6, with TMS as an internal standard.

General procedure for synthesis of 2, 4, 5-triaryl imidazoles from 1, 2-diketones (1a) or α-hydroxyketone (1b)

A mixture of 1, 2-diketones (la) or the α-hydroxyketone (1b) (1 mmol), substituted aldehydes (2a-h,1mmol), ammonium acetate (10 equiv) and CAN (5 mol%) was reflux at 75°C for the appropriate time mentioned in Table 2. The completion of reaction was monitored by TLC using ethyl acetate: petroleum ether (1:9). After completion of reaction, the reaction mixture was diluted with water. The solid imidazole products, which separated out, were filtered, washed with sodium bisulphate and dried. The crude products, thus isolated, were pure (single spot on TLC). They were subjected to further purification by column chromatography 10% EtOAc in petroleum ether used as eluent to yield the desired substituted imidazoles in excellent yields of 86-92%.

SPECTRAL DATA

2-(4, 5 -Diphenyl -1*H*-imidazol-2-yl)-6-methoxy phenol (3a). MP 168^{o}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 (brs, IH); ^{l3}C NMR (CDCl,/DMSO-d_6, 200 MHz) 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): calcd C. 77.17, H. 5.30, N. 8.18; found C. 77.08, H. 5.18, N. 8.02.

2-(4-Methoxy-phenyl)-4, 5-diphenyl-l*H* -imidazole (3b). Mp 220 ^{o}C; IR (cm^{-1}) 1216, 1636, 2465, 2893. 3428; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.85 (s, 3H), 6.93-6.96 (d, *J* = 8.8 Hz. 2H), 7.25-7.59 (m, 10H), 8.02-8.05 (d, J = 8.7 Hz, 2H). 12.52 (brs, IH); ^{13}C NMR ($CDCl_3$ d_6/DMSO-d_6, 200 MHz) δ 54.6, 113.2, 122.7, 126.3, 126.5, 127.4, 127.6, 132.8, 145.7 159.1; $C_{22}H_{18}N_2O$ (326): calc C. 80.96, H. 5.56, N. 8.85; found C. 80.85, H. 5.48, N. 8.38.

2-(4, 5-Diphenyi-l*H* -imidazol-2-yl)-2-methoxy phenol (3c). Mp 195 °C; IR (cm^{-1}) 1230, 1450, 1605, 2924, 3512, 3614; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.80 (s, 3H), 6.75-6.69 (d, *J* = 8.22 Hz, IH), 7.11-7.19 (m, 5H), 7.22-7.23 (d. *J* = 8 Hz, IH), 7.40-7.45 (m, 5H), 7.55-7.56 (d, *J*= 8 Hz, IH), 12.52 (brs, IH); ^{13}C NMR (CDCl3/DMSO-d_6, 200 MHz) δ 55.1, 108.5, 114.6, 118.1, 121.1, 126.2. 127.3, 127.5, 132.3, 146.3, 146.8; $C_{22}H_{18}N_2O_2$ (342): calcd C. 77.17, H. 5.30, N. 8.18; found C. 77.05, H. 5.18, N. 8.02.

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2-(4, 5-Diphenyl-l*H*-imidazol-2-yl)-phenol(3d). Mp 205°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*=7.5 Hz, 2H), 6.96-7.01 (d, *J* = 8.06 Hz, 2H), 7.17-7.23 (m, 10H), 12.74 (brs, IH); ^{I3}C NMR ($CDC1_3$/DMSO- d_6, 200 MHz) *d* 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): calcd C. 80.75, H. 5.16, N. 8.97; found C. 80.62, H. 5.08, N. 8.85.

4-(4, 5-Diphenyl-l *H* -imidazol-2-yl)-phenol (3e). Mp 231°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 (brs, IH); ^{I3}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): calcd C. 80.75, H. 5.08, N. 8.97; found C. 80.68, H. 5.05, N. 8.90.

2-(4-Methyl-phenyl)-4, 5-diphenyl-l*H* -imidazole (3f). Mp 158-161°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 (CD Cl_3 /DMSO-d_6, 200MHz) 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 (3g). Mp 198-200 °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=9Hz, 1H), 8.22 (d, j=9Hz, 1H), 7.76 (t, 1H), 7.25-7.5 (m, 10H); ^{13}C NMR (CD Cl_3 /DMSO-d_6, 200MHz) 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 (3h). Mp 237-240°C; 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 (CD Cl_3 /DMSO-d_6, 200MHz) 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.

Table1 Effect of catalytic amount of CAN[b]

[a]Entry	[b]Catalyst	Amount (mol%)	Time(hrs)	Yield(%)[d] 1a 1b
1	NO	-	5	ND[c] ND[c]
2	CAN	5	5	90 91
3	CAN	10	5	75 78
4	CAN	20	5	73 70
5	CAN	25	5	85 87
6	CeSO4	20	7	60 58

[a]Entry 1-6 .[b]CAN Ceric ammonium nitrate[$(NH_4)Ce(NO_3)$], [c]ND no product formation, [d] isolated yield 1a(benzil) 1b(benzoin) obtained by column chromatography.

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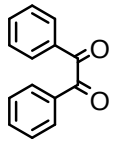
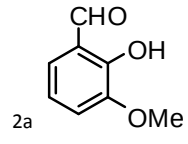
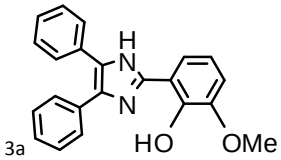
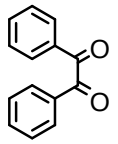
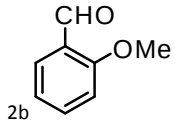
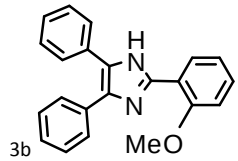
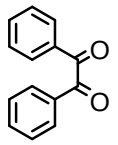
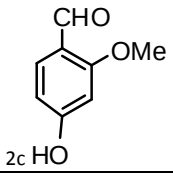
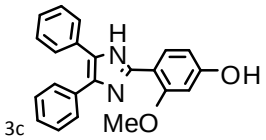
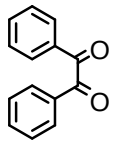
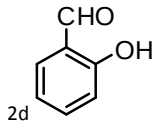
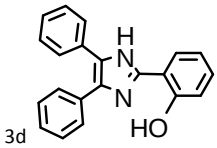
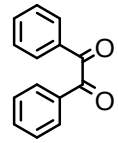
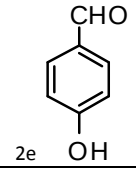
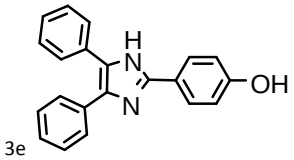
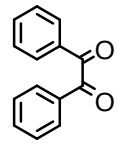
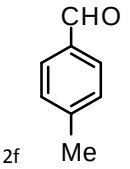
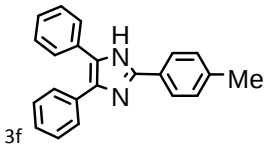
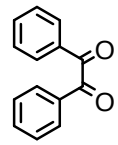
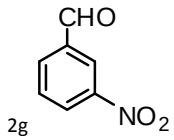
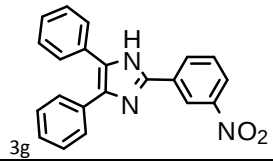
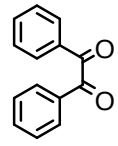
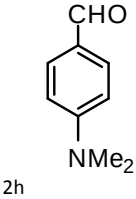
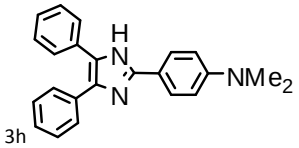
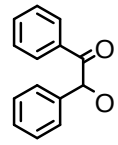
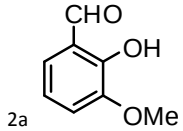
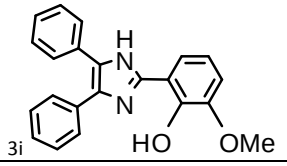
Table 2 Synthesis of 2, 4, 5 – triaryl imidazoles from 1, 2-diketones (1a) or α-hydroxyketone (1b)

Reactant 1a,1b	Reactant 2	Product 3	Time(h)	Yield(%)
	 2a	 3a	4	90%
	 2b	 3b	3	91%
	 2c	 3c	3	90%
	 2d	 3d	1.5	89%
	 2e	 3e	4	92%
	 2f	 3f	5	91%
	 2g	 3g	4.5	89%
	 2h	 3h	3.5	92%
	 2a	 3i	4	90%

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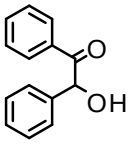
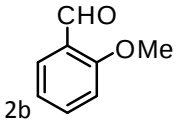
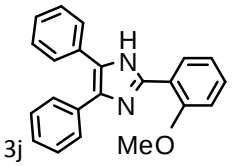
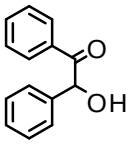
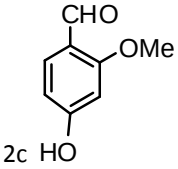
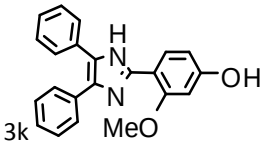
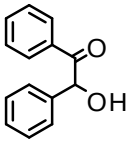
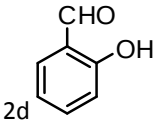
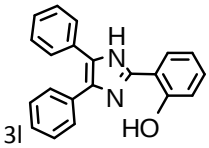
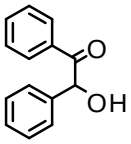
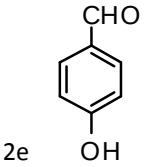
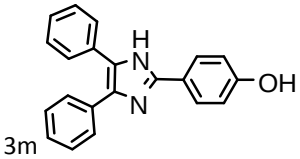
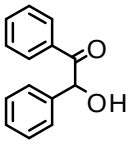
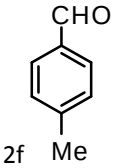
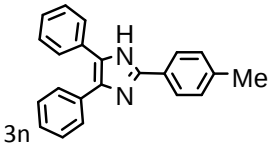
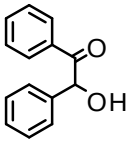
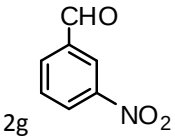
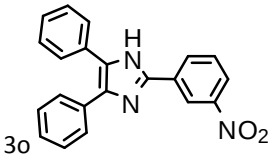
	 2b	 3j	4	90%
	 2c	 3k	3	92%
	 2d	 3l	4	89%
	 2e	 3m	4	91%
	 2f	 3n	5	90%
	 2g	 3o	4	89%

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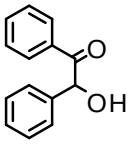
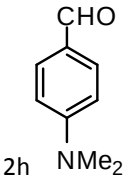
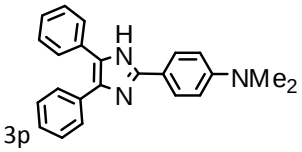
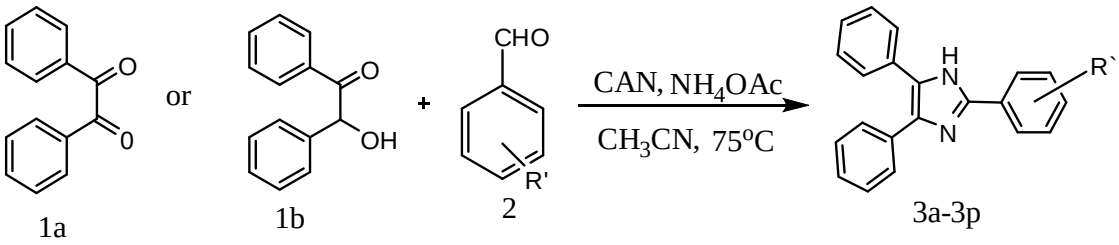
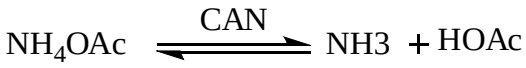
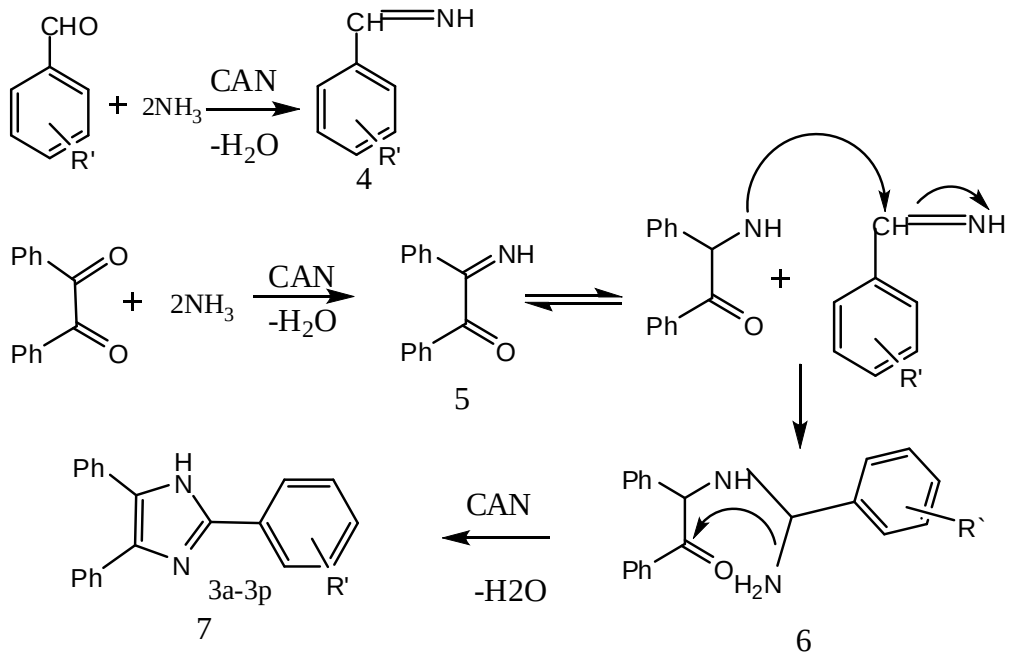
	 2h	 3p	3.5	88%



Scheme:-1 Synthesis of triarylimidazoles





Schem 2 plausible mechanism for the formation of triarylsubstituted imidazole 3a-3p

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