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Mechanostic Synthesis of Antimicrobial Imidazoles

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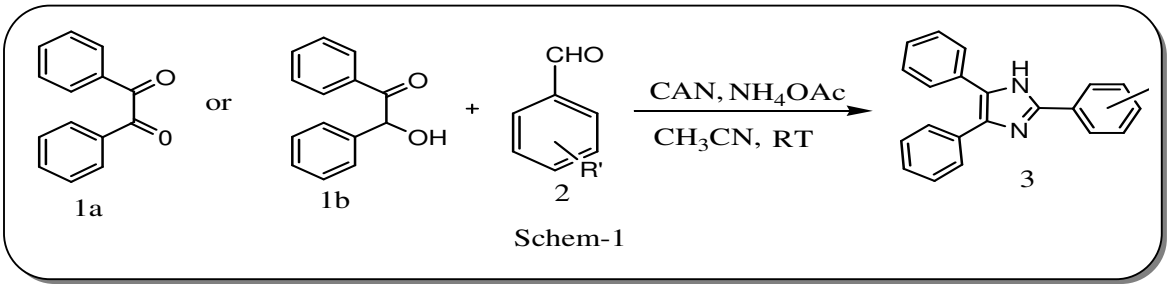
Introduction:

Interest in the imidazole nucleus is their widespread biological activities and their use in synthetic chemistry. Imidazole produces histamine[1] in metabolic process. The potency and 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 [7], imidazoles also have COX-2 inhibitory activity[8]. Literature survey reveals that there are several methods for synthesizing triaryl imidazoles and 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[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]. Previous methods have one or the other limitations such as, poor yields prolonged time period, use of hazardous and expensive catalysts, harsh reaction conditions and polar solvents. Nowadays ceric ammonium nitrate (CAN) received focus of researchers because it is 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 aldehydes at room temperature in the presence catalytic amount of CAN **scheme1**[25] which we have reported already but at reflux condition. During the course of our studies toward the development of new routes to the synthesis of biologically active heterocycles[22].



Schem-1

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. 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** .

Table:-1 Effect of catalytic amount of CAN[b]

[a]Entry	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 [$(NH_4)Ce(NO_3)$], ND[c] no product formation,

[d]1a isolated yield 1a(benzil) ,1b(benzoin) obtained by column chromatography.

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 **Table 1**. 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°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.

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

$$NH_4OAc \underset{}{\overset{CAN}{\rightleftharpoons}} NH3 + HOAc$$

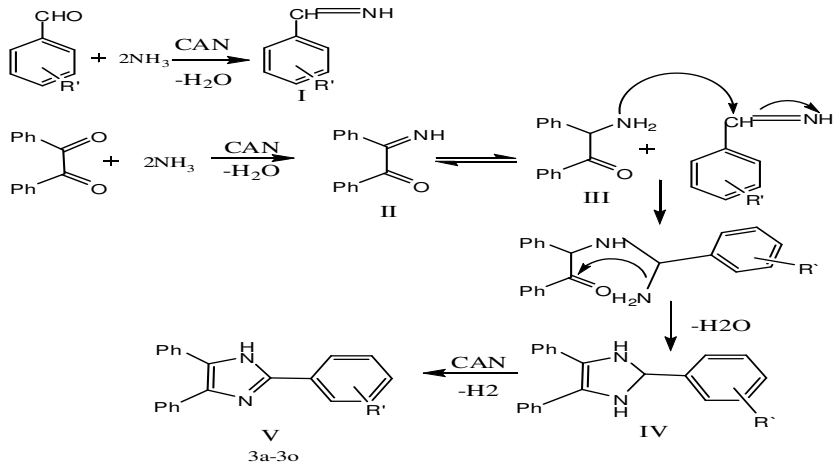
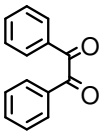
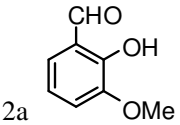
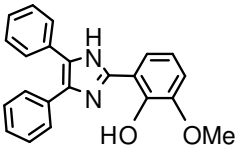
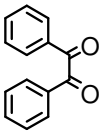
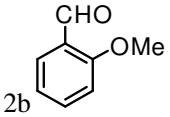
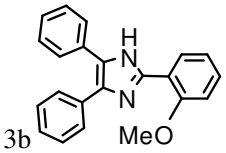
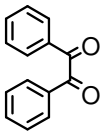
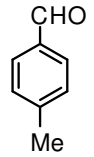
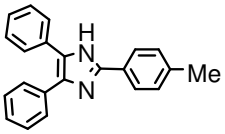
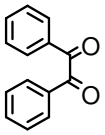
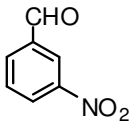
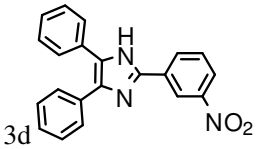
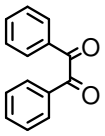
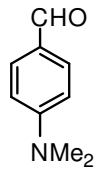
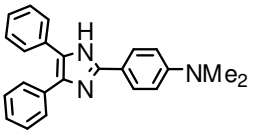


Table:-2 Synthesis of 2,4,5 trisubstituted imidazol from 1a benzyl or 1b benzoin

Reactant 1a,1b	Reactant 2	Product 3	Time(h)	Yield(%)
	 2a	 3a	2	92%
	 2b	 3b	1.5	91%
	 2c	 3c	4	87%
	 2d	 3d	2.5	92%
	 2e	 3e	1.5	90%

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) at room temperature **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).

Antibacterial screening:

The antibacterial activities of the synthesized compounds (3d) and (3e) were studied against four bacteria, viz. Bacillus subtilis (G+), Escherichia coli (G–),Staphylococcus aureus (G+) and Pseudomonas aeruginosa (G–). For the detection of antibacterial activities, the filter paper discs diffusion method was used[26]. Streptomycin sulphate was used as positive control. Nutrient agar (NA) was used as basal medium for test bacteria. The discs were prepared by impregnating them in methanol solution of each sample (1 mg/1 mL). Each culture was prepared to a turbidity equivalent to McFarland and spread on the test tube. The paper disc containing the compound was placed on the agar surface previously inoculated with suspension of each microbe to be tested. All determinations were made in duplicate. Inhibition diameter was determined after incubation at 37°C ± 1 for 24 h. The antimicrobial activity was indicated by the presence of the clear inhibition zones around each disc.

Minimum inhibition concentration:

The determination of the minimum inhibitory concentration (MIC), the serial dilution technique was followed using nutrient broth medium. The MIC was defined as the lowest concentration of samples that had restricted the growth of microbial[27]. The MIC value of compound (d) were determined against Escherichia coli (G–).

In conclusion, we have developed an efficient, convenient and one-pot protocol for the synthesis of bioactive compounds 2, 4, 5-triaryl Imidazoles via the condensation of aromatic aldehydes and benzil or benzoin with ammonium acetate using ceric ammonium nitrate. The process gives rise to excellent isolated yield of triaryl imidazole.

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) spectrometer in $CDCl_3$/DMSO-d6, with TMS as an internal standard.

Table 3. Antibacterial screening for the compounds (3d) and (3e) Diameter of the zone of inhibition (mm)

Organism	Benzyl+aldehyde	2,4,5 trisubstituted imidazol	Streptomycin sulphate
Bacillus subtilis	–	-	22·0 ± 0·3
Staphylococcus aureus	-	-	22·5 ± 0·7
Escherichia coli	-	12·5 ± 0·3	22·0 ± 0·0
Pseudomonas aeruginosa	-	-	22·0 ± 0·0

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 (1a) or the α-hydroxyketone (1b) (1 mmol), substituted aldehydes (2a-h,1mmol), ammonium acetate (10 equiv) and CAN (5 mol%) was stir at room temperature 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%.

Antibacterial screening:

The antibacterial activity of compounds (3d) and (3e) has been assayed at the concentration 1000 μg/mL against four human pathogenic bacteria. Among them two were gram-positive and the other two were gram negative. The inhibitory effect of compounds (3d) and (3e) against these organisms are given in table 3.The screening results indicate that only compound (3g) was active against a gram-negative bacteria, Escherichia coli with a mean zone of inhibition 12·5 ± 0·3 mm (table 3).

Determination of the minimum inhibitory concentration (MIC) :

The active sample in the disc diffusion method was then tested for its activity by the serial dilution method to determine the minimum inhibition concentration (MIC-value). The MIC value obtained for substituted imidazoles (3d) was 1000 μg/mL against Escherichia coli.

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