Zn(OAc)₂•2H₂O-catalyzed one-pot synthesis of divergently substituted Imidazoles

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C H R O N I C L E	A B S T R A C T
	Wide range of 2,4,5-trisubstituted imidazoles were synthesized using eco-friendly, readily available, inexpensive Zn(OAc)₂•2H₂O (5 mol%) under solvent-free conditions in moderate to excellent yields by condensation from aldehyde, ammonium acetate and benzil at 70 ^{0}C. The optimized reaction parameters were successfully applied for the synthesis of divergent 1,2,4,5-tetrasubstitued imidazoles using aromatic amine as fourth component. All the imidazole derivatives were sufficiently characterized by IR, NMR and Mass spectral analyses.

1. Introduction

By carrying out several reactions in a single reaction step, multi-component reactions (MCRs) have a high potential for constructing a variety of small bioactive scaffolds with outstanding structural/atom economy. Additionally, they are useful tools for creating heterocyclic motifs that are biologically and pharmaceutically active.[1-3] Heterocyclic compounds are very important organic molecules and constitute the largest diversity of chemical compounds with a high industrial significance.[4-7] For minimizing the production costs and operational simplicity, applications of solvent-free based synthetic strategies to meet the greener synthesis of pharmacologically relevant molecules have picked up some momentum.[8-9]

Since the dawn of time, substances containing imidazoles have been extensively studied. It therefore represents a major portion of the new medication development. Antifungal, antiepileptic, ACE inhibitors, and other drugs with an imidazole moiety have all been produced, studied, and marketed for the treatment of various ailments.[10-12] Additionally, imidazoles play a significant role in the synthesis of natural substances such biotin, vitamin B12, histamine, and histidine. Rani et al. recently reviewed the marketed drugs possessing imidazole moiety, as shown in the **Fig. 1**.[13] An organic molecule with imidazole derivatives has acquired a sustainable place in medical and clinical fields. The consolidation of the imidazole unit is a significant synthetic technique in drug development. Due to their low vapour pressure and temperature stability, imidazole derivatives are employed as task-specific ionic liquids (TSIL), which are then used as catalysts and green solvents.[14] In photography, photosensitive imidazole compounds are employed.[15]

Losartan
(an anti-hypertensive agent)

Eprosartan
(an anti-hypertensive agent)

Cimetidine
(an anti-ulcerative agent)

Ketoconazole
(an anti-androgen and anti-fungal)

Trifenagrel
(an arachidonate COX inhibitor)
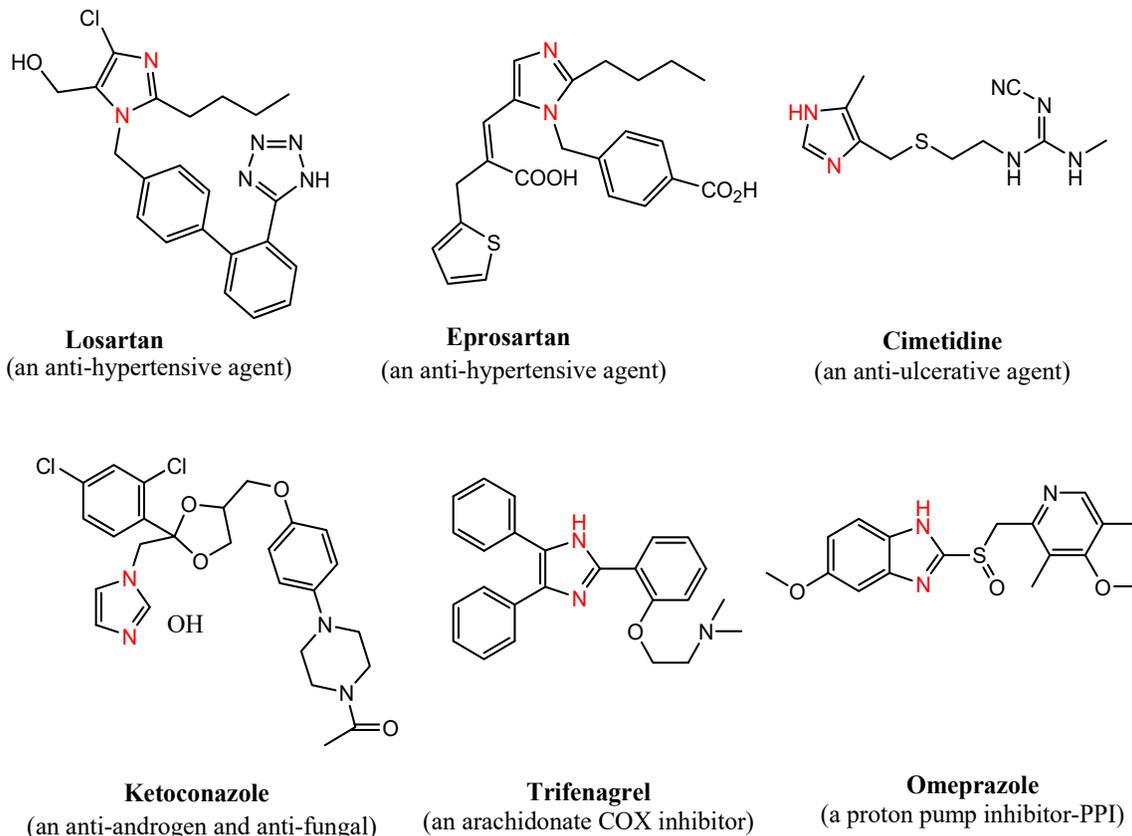
Omeprazole
(a proton pump inhibitor-PPI)

Fig. 1. Few marketed drugs having imidazole scaffold

Keeping in view of the importance of imidazole moiety, various synthetic methodologies are being developed as a continuous process for achieving better atom economy, eco-friendly and cost-effectiveness and several recent reviews[16-19] and research articles[20-24] have well documented the same. Toxic transition metal catalyst, protic acids, extended reaction durations, high temperatures, low to moderate yields, volatile organic solvents, and the majority of methods of production for tri and tetraarylimidzoles have above disadvantages. Therefore, a superior catalytic system in a clean, environmentally friendly environment is preferred.

The Zn-based complexes were previously used in various catalytic reactions.[25-28] Enthaler and Wu thoroughly discussed applications of zinc in organic synthesis, encompassing a variety of chemical transformations.[29] After thorough literature search, we found that $Zn(OAc)_2 \cdot 2H_2O$ has not been exploited for the target reaction. Among a multitude of zinc complexes, zinc acetate ($Zn(OAc)_2$) is readily available and stable under ambient conditions in the presence of moisture and air.[30-42] Several reports demonstrating the catalytic efficiency of $Zn(OAc)_2 \cdot 2H_2O$ prompted us to perform the reactions to synthesize both 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles (**Schemes 1** and **2**).

Scheme 1. $Zn(OAc)_2 \cdot 2H_2O$-catalyzed synthesis of 2,4,5-trisubstituted imidazoles
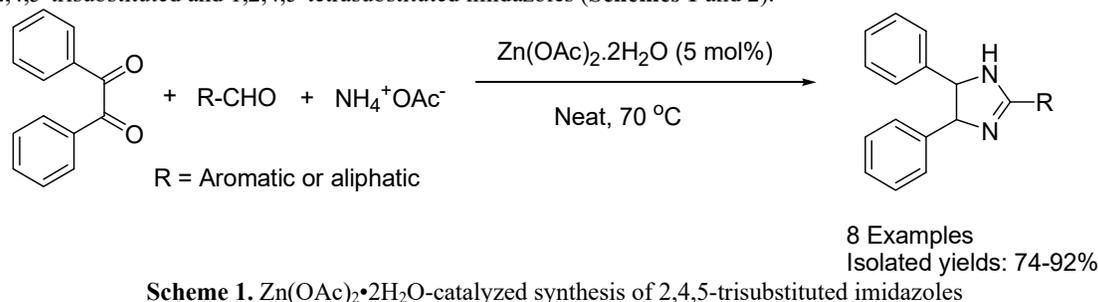
2. Results and Discussion

Initially, the three component condensation reaction was screened for benzil (1 mmol), ammonium acetate (2 mmol) and benzaldehyde (1 mmol) as substrates for the model reaction and ethanol as solvent in the presence of $Zn(OAc)_2 \cdot 2H_2O$ (10 mol%) at ambient temperature (**Table 1**). The reaction mixture was stirred for a period of 24 h and based on TLC and further purification, only little amount of corresponding imidazole formation (17%) was observed (entry 1, Table 1). The reaction temperature is considered as a significant factor in assessing the feasibility of chemical reactions. It is crucial in

the context of one-pot MCR reactions since extremely high temperatures typically result in the creation of several undesirable byproducts. Therefore, we carried out a cyclocondensation reaction while adjusting the temperature from 40 ^{0}C to 100 ^{0}C by increments of 10 ^{0}C. The maximum yield of 89% was obtained at 70 ^{0}C, and the temperature above 70 ^{0}C had no discernible effect on the product yield.

Table 1. Study of temperature parameter

Entry	Temp (^{0}C)	Time (h)	Yield (%)[a]
1	r.t	24	17
2	40	12	32
3	50	2	38
4	60	12	51
5	**70**	**0.45**	**89**
6	80	1	83
7	90	1	82
8	100	1	81

[a]Isolated yields

Zn(OAc)$_2$•2H$_2$O was used as the catalyst for the reaction, which was conducted at 70 ^{0}C in a variety of solvents including toluene, acetone, ethanol, chloroform, acetonitrile, and neat conditions (**Table 2**). We found that, compared to the reaction performed in chosen solvents, solvent-free conditions afforded the corresponding product in excellent yield (entries 6-8, Table 2). Moreover, 5 mol% of the catalyst was found to be sufficient to carry forward the reaction to afford maximum isolated yield (entry 7, Table 2).

Table 2. Study of solvent and catalyst loading

Entry	Solvent	Yield[a] (%)
1	Toluene	72
2	Acetone	28
3	Ethanol	65
4	Acetonitrile	47
5	Chloroform	29
6	Neat (Zn(OAc)$_2$•2H$_2$O, 10 mol%)	89
7	**Neat** (Zn(OAc)$_2$•2H$_2$O, 5 mol%)	**92**
8	Neat (Zn(OAc)$_2$•2H$_2$O, 2.5 mol%)	82

[a]Isolated yields

Different zinc salts were used for the cyclocondensation reaction of benzaldehyde, benzil, and ammonium acetate under solvent-free conditions to show the effectiveness of Zn(OAc)$_2$•2H$_2$O as catalyst. The obtained results were presented in **Table 3**. It is observed that for all other zinc salts used as catalysts, low conversion of 2,4,5-trisubstituted imidazoles was achieved. The stability of the other catalysts during and after the reactions has not been studied in this preliminary communication as the catalytic ability of Zn(OAc)$_2$•2H$_2$O was superior to other zinc salts tested in terms of isolated yields and reaction time (entry 6, Table 3). The superior catalytic activity of Zn(OAc)$_2$•2H$_2$O for the intended reaction optimization has not been investigated or performed for the effective surface area studies based on BET measurement.
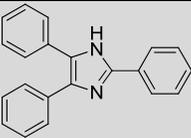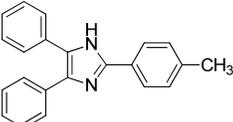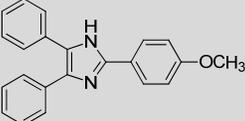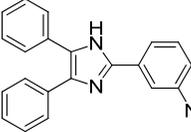
Table 3. Effect of catalyst on synthesis of trisubstituted imidazoles

Entry	Zinc salt	Reaction Time (h)	Yield[a] (%)
1	ZnSO4	24	09
2	Zn(NO3)2	6	21
3	ZnBr2	6	45
4	ZnCl2	6	47
5	Zn(OTf)2	2	75
6	**Zn(OAc)$_2$•2H$_2$O**	**1**	**92**
7	Zn(l-proline)2	6	37
8	Zinc dust	8	42
9	Zn^{2+}-mont	4	58
10	Zn hydroxyapatite	4	62

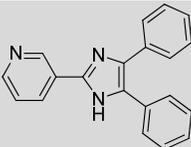[a]Isolated yields

To test the efficacy of this condensation process, a series of 2,4,5-trisubstituted imidazoles were synthesized from benzil, ammonium acetate, and various aldehydes, in the presence of 5 mol% Zn(OAc)$_2$•2H$_2$O under neat conditions at reflux temperature (**Table 4**). Both electron-donating and electron-withdrawing groups found in aromatic aldehydes were well tolerated (entries 2-6, Table 4). Interestingly, highly substituted imidazoles were generated in moderate yields by the reaction using heterocyclic aldehydes such as pyridine 3-carboxaldehyde and thiophene 2-carboxaldehyde (entries 7-8, Table 4). Alkyl aldehyde, such as propionaldehyde and isobutyraldehyde also underwent reaction to give the corresponding products in moderate yields (entry 9-10, Table 4).

Table 4. Zn(OAc)$_2$•2H$_2$O-catalyzed synthesis of 2,4,5-trisubstituted imidazoles

Entry	Aldehyde	Product	Time (h)	Yield (%)[a]/ Ref.[20,22, 24]
1	Benzaldehyde		1	92
2	4-Methyl Benzaldehyde		1	89
3	4-Methoxy benzaldehyde		1	95
4	3-Nitro benzaldehyde		2	79
5	4-Hydroxy benzaldehyde		2.5	80
6	4-Bromobenzaldehyde		2	88
7	3-Pyridine carbaxaldehyde		3	72
8	2-Thiphene carboxaldehyde		3	68
9	Propoinaldehyde		3	62
10	Isobutyraldehyde		3	58
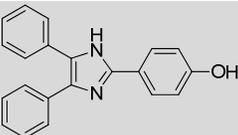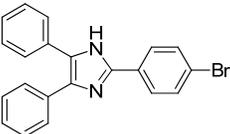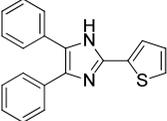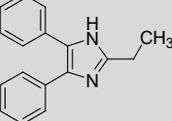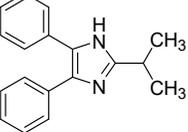
[a]Isoalted yields

Following the success of the three component reaction, we focused on assessing the viability of our methodology for the synthesis of tetrasubstituted imidazole derivatives using four component reactions under the same reaction conditions with the addition of a stoichiometric ratio of various aromatic amines as the fourth component (**Scheme 2**).
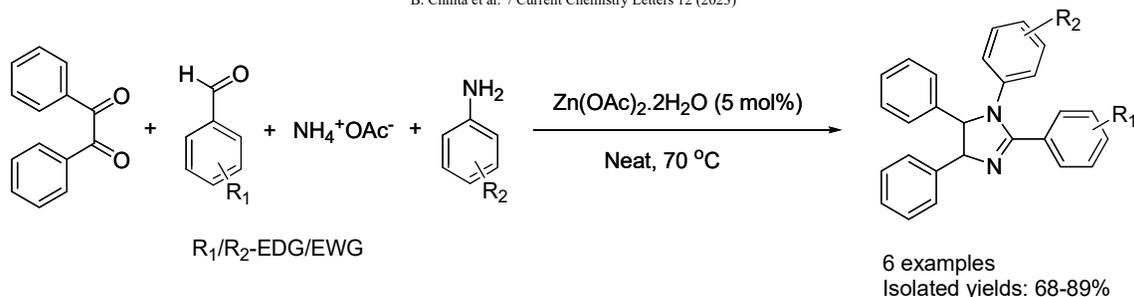
Scheme 2. Zn(OAc)$_2$•2H$_2$O catalyzed Synthesis of 1,2,4,5-trisubstituted imidazoles

To our surprise, the reaction proceeded without issue, regardless of the nature or electronic impact of the substituent on the aromatic rings, and excellent yields were achieved for the desired tetrasubstituted imidazole compounds (**Table 5**). These findings demonstrate that reactions involving aniline or aldehyde groups with electron-donating alkyl and alkoxy groups, such as those involving toluene and anisidine (Table 5, entries 2-4), proceeded without difficulty and produced high yields. Utilizing anilines with electron-withdrawing groups, such as chloroaniline and nitroaldehyde, the reaction rate is decreased slightly (entries 5-6, Table 5).

Table 5. Zn(OAc)$_2$•2H$_2$O-catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles

Entry	R$_1$	R$_2$	Product	Time (h)	Yield (%)[a]/Ref.[20,22,24]
1	H	H		1.5	90
2	4-CH$_3$	4-OH		1	82
3	4-OH	4-OCH$_3$		2.5	88
4	4-OH	4-CH$_3$		2.5	80
5	H	2-Cl		1.25	78
6	3-NO$_2$	H		3	68

[a]Isoalted yields

In order to facilitate the nucleophilic addition of ammonia cross polarised C=O, it is speculated that the catalyst Zn(OAc)$_2$•2H$_2$O increases the electrophilicity at the carbon atom of the carbonyl group of the aldehyde. This, in turn, facilitates the formation of the diamine intermediate (**4**) by dehydration. After the elimination of water and cyclocondensation of intermediate (**4**) with benzil, intermediate (**7**) is produced. This intermediate then goes through a [1,5] proton shift to create 2,4,5 triarylimidzole (**8**) (**Scheme 3**).
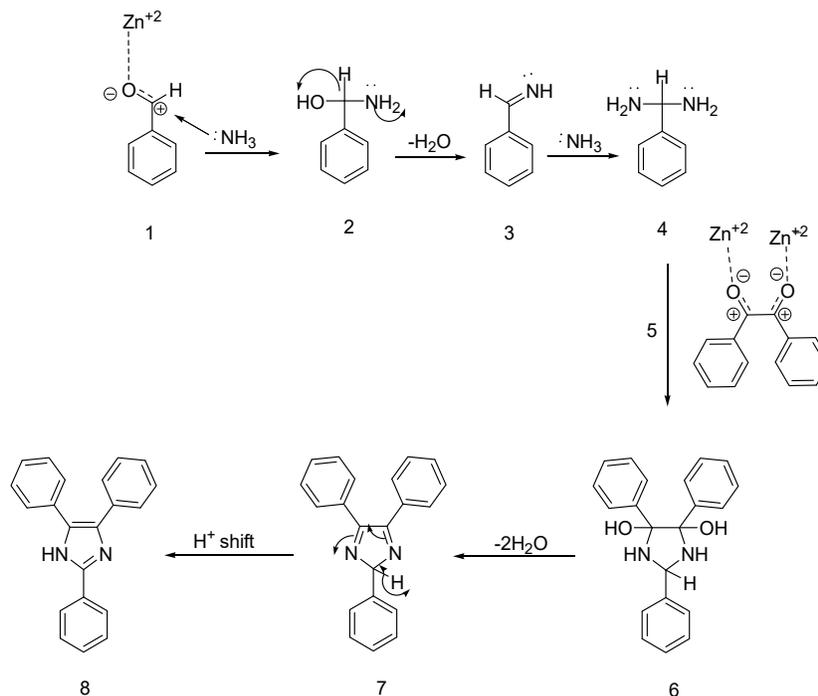
Scheme 3. Mechanism of synthesis of trisubstitutedimidazoles

3. Conclusions

In this work, Zn(OAc)$_2$•2H$_2$O was successfully employed as the green, readlily available and cost-effective catalyst for the one-pot, three-component cyclocondensation of benzil, aromatic aldehydes, and ammonium acetate under neat conditions for the first time. The new approach has a number of advantages over the traditional method for making tri- and tetra-aryl imidazoles, including increased product conversion and the absence of undesirable side products.

4. Experimental

Materials & Methods

Without additional purification, all of the chemicals were purchased from commercial sources and used. Prior to use, chromatography solvents were distilled. On Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) instruments, ^{1}H and ^{13}C NMR spectra were captured in DMSO-d_6. Chemical shifts are expressed as parts per million () in relation to the internal standard, tetramethylsilane (δ 0.0). On a VG 7070H Micromass mass spectrometer, electron-impact (EI) mass spectra were captured at 200 °C and 70 eV. Elementar analyzer Vario EL carried out the elemental analysis. An electrothermal melting point instrument has been used to record melting points. The IR spectra were collected using potassium bromide pellets/neat and a Perkin Elmer 240-C instrument. On Merck precoated plates, analytical TLC of all reactions was carried out (silica gel 60F-254 on glass). Acme silica gel was used for column chromatography (100-200 mesh).

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles (Scheme 1)

In a 10 ml round bottom flask, the following substances were combined neat: aromatic aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (2 mmol), and Zn(OAc)$_2$•2H$_2$O (5 mol %). The mixture was then heated and maintained at 70 °C with stirring for the appropriate time, and the reaction's progress was observed using TLC. The reaction mixture was cooled to room temperature after the reaction was finished, as shown by TLC. With 5 mL of water, the reaction mixture was diluted. The product was extracted with 2x5 mL of ethyl acetate.

By using anhydrous MgSO$_4$, the organic layer was dried. The product was refined either by recrystallizing in hot ethanol or by column chromatography on silica gel (60-120 Mesh, 20% EtOAc/Petroleum ether mixture) after the organic layer had been concentrated under vacuum. Through the use of FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrum analysis, each product was sufficiently characterized and compared with literature data[20-24]

2,4,5-Triphenyl-1*H*-imidazole

White solid; mp: 277-279 °C; IR (neat, cm^{-1}): 3215 (N-H), 3057 (C-H, Ar), 1627 (C=N),1589 (C=C); ^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 12.70 (s, 1H , N-H), 8.10 (d, 2H, Ar-H), 7.57-7.23 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 145.97, 137.55, 135.62, 131.55, 130.81, 129.17, 128.77, 127.54, 127.00, 125.66; Mass (*m/z*): Calcd for C$_{21}$H$_{16}$N$_2$: 296.13; Found: 294.07.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Scheme 2)

The mixture of aromatic aldehyde (1 mmol), aromatic primary amine (1 mmol), benzil (1 mmol), ammonium acetate (1 mmol), and Zn(OAc)$_2$•2H$_2$O (5 mol %) under solvent-free conditions was taken in a 10 ml round bottom flask, heated to 70 °C, and kept there while being stirred for the appropriate amount of time. TLC was used to monitor the reaction's progress. The reaction mixture was cooled to room temperature when the reaction was finished, as shown by TLC. The reaction volume was reduced and diluted with 5mL of water. The product was extracted with 2x5 mL of ethyl acetate. By using anhydrous MgSO$_4$, the organic layer was dried. The product was purified either by recrystallizing in hot ethanol or by column chromatography on silica gel after the organic layer was concentrated under vacuum. Through the use of FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrum analysis, each product was fully characterized and compared with literature data[20-24]

1,2,4,5-tetraphenyl-4,5-dihydro-1*H*-imidazole

White solid; mp: 277-279 ^{0}C; IR (neat, cm^{-1}): 3061 (C-H aromatic), 1659 (C=C, aromatic), 1595 (C=N); ^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 7.96-7.80 (m, 6H, Ar-H), 7.67-7.61 (m, 3H, Ar-H), 7.58-7.52 (m, 6H, Ar-H), 7.46-7.40 (m, 2H, Ar-H), 7.39-7.20 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 161.19, 151.93, 146.51, 137.59, 136.48, 135.71, 134.87, 132.70, 131.96, 130.82, 129.99, 128.90, 127.55, 126.98, 125.67, 121.45, 114.32; Mass (*m/z*): Calcd for C$_{18}$H$_{18}$N$_2$: 372.46, Found: 371.81

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