One-Pot Efficient Synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles and 2,4,5-Triaryl-1*H*-imidazoles Using Oxalic Acid Catalyst

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Received 12 March 2007; revised 19 June 2007

Abstract: Oxalic acid was found to be a versatile catalyst for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles and 2-aryl-4,5-diphenyl-1*H*-imidazoles in moderate to excellent isolated yields. 2-Aryl-1-arylmethyl-1*H*-benzimidazoles were efficiently synthesized from *o*-phenylenediamine and various substituted aldehydes using 10 mol% oxalic acid. 2-Aryl-4,5-diphenyl-1*H*-imidazoles were synthesized from benzil or benzoin, ammonium acetate, and aromatic aldehydes. The advantages of this method are the use of an inexpensive and readily available catalyst, easy workup, and improved yields, and the use of an ethanol–water solvent that is considered to be relatively environmentally benign.

Key words: oxalic acid, 2-aryl-1-arylmethyl-1*H*-benzimidazole, 2,4,5-triaryl-1*H*-imidazole, benzoin, benzil, aromatic aldehydes

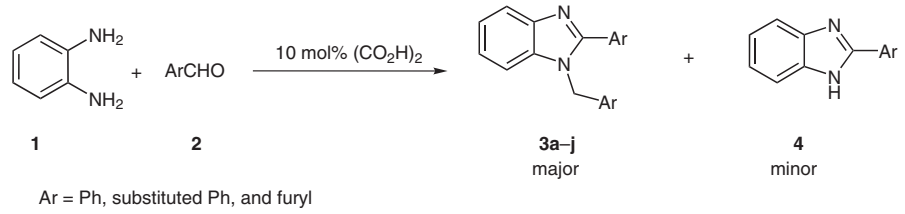
Interest in benzimidazole-containing structures stems from their widespread occurrence in molecules that exhibit significant biological activity against several viruses such as HIV, herpes (HSV-1), RNA, influenza, and human cytomegalovirus (HCMV).[1] In addition, benzimidazole derivatives show fungicidal, antitumor, immunosuppressant, and anticonvulsant properties.[2] Since benzimidazoles are commonly used as intermediates in synthetic routes and serve as ligands for the asymmetric catalysis,[3] the preparation of benzimidazole has importance. A literature survey reveals several methods for synthesis of benzimidazole and its derivatives. Commonly, it is prepared by the condensation of *o*-phenylenediamine with carboxylic acids or their derivatives with heating at high temperature.[4] The use of different transition metal catalysts for the preparation of benzimidazole has substantially increased. The methods involve palladium-catalyzed carbonylation reaction of *o*-phenylenediamine followed by cyclodehydration; palladium-catalyzed intermolecular N-arylation reaction.[5] An alternative approach is the condensation of aldehydes with *o*-phenylenediamine using various catalysts [e.g., mild Lewis acids[6] or triflate salts such as $Sc(OTf)_3$ and $Yb(OTf)_3$].[7] The TOP methodology was reported for preparation of substituted benzimidazoles using activated alcohols, *o*-phenylenediamine, and oxygen or manganese(IV) oxide as oxidant.[8] The SET reaction of 2-nitroaniline with benzaldehyde in the presence of indium/2-bromo-2-nitropropane and reductive cyclizations of *o*-nitroaniline with aldehydes in the presence of sodium dithionite have also been used for synthesis of the benzimidazole derivatives.[9] However, many of these methods have several drawbacks such as expensive reagents, oxidation processes, and prolonged reaction times. In some cases, 2-substituted and 1,2-disubstituted benzimidazole were generated simultaneously with poor selectivity. In connection with our ongoing research for the development of simple and efficient methods for synthesis of heterocyclic compounds,[10] we now report an efficient and practical method for the one-pot synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles using oxalic acid as a catalyst.

Oxalic acid is the only possible compound containing two carboxylic groups joined directly; and hence it is a strong organic acid. The use of oxalic acid as a catalyst was reported for the deprotection of ketals to give the corresponding aldehydes or ketones[11] and the isomerization of Δ^5-cholesten-3-one to D^4-cholesten-3-one.[12] Oxalic acid is also used for the dealumination of zeolite.[13] We have used oxalic acid (10 mol%) for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles **3** under mild reaction conditions.

Table 1 Optimization of Reaction Conditions for the Synthesis of 1-Benzyl-2-phenyl-1*H*-benzimidazole (**3a**)

Solvent	Oxalic acid (mol %)	Time (min)	Yield (%)
CH_2Cl_2	20	55	76
THF	20	50	87
MeCN	20	50	83
EtOH	20	40	87
THF–H_2O (1:1)	20	45	93
MeCN–H_2O (1:1)	20	35	91
EtOH–H_2O (1:1)	20	30	96
EtOH–H_2O (1:1)	15	35	96
EtOH–H_2O (1:1)	10	35	96
EtOH–H_2O (1:1)	5	65	88
EtOH–H_2O (1:1)	2.5	85	73

SYNTHESIS 2007, No. 18, pp 2829–2834
Advanced online publication: 29.08.2007
DOI: 10.1055/s-2007-983872; Art ID: Z06307SS



Scheme 1 Synthesis of 1,2-disubstituted benzimidazoles

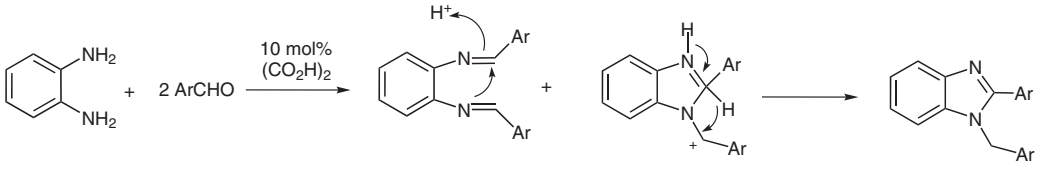
Initially, we studied the catalytic efficiency of oxalic acid for a model reaction using *o*-phenylenediamine (**1**) and benzaldehyde (**2a**) in different solvents and various mol% of oxalic acid at ambient temperature (Scheme 1, Table 1). 1-Benzyl-2-phenyl-1*H*-benzimidazole (**3a**) was isolated in 96% yield using optimized reaction conditions, which utilized ethanol–water (1:1) as the solvent and 10 mol% of oxalic acid catalyst. Using the optimized reaction conditions, a range of 1,2-disubstituted benzimidazoles **3a–j** were synthesized (Table 2). This method was found to be equally effective for aldehydes bearing either electron-donating (Table 2, entry 2) or electron-withdrawing substituents (Table 2, entries 7, 8). The advantage of this method is its easy workup, which includes pouring of the reaction mixture into ice water to precipitate a solid, which is filtered off to give sufficiently pure compounds in good yields. The products were isolated in better yields and in less reaction time than previously reported methods.[14] In particular, 1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (**3c**) was prepared in 95% yield in 35 minutes (Table 2, entry 3) compared to the reported yield of 72% in 5.5 hours.[14a]

The selectivity observed for the synthesis of 1,2-disubstituted benzimidazoles **3a–j** was good. When using two equivalents of benzaldehyde, exclusively formation of 1-benzyl-2-phenyl-1*H*-benzimidazole (**3a**) was observed. To check the selectivity, the reaction was carried out using one equivalent of benzaldehyde and *o*-phenylenediamine and product obtained was analyzed by HPLC. The percentages of products **3** and **4** found were 92% and 8% respectively, which shows the selectivity for the disubstituted benzimidazole product **3a**.

The proposed mechanism for synthesis of the 1,2-disubstituted benzimidazoles **3** may involve the iminium-catalyzed formation of an *N*,*N*′-dibenzylidene-*o*-phenylenediamine, protonation, and ring closure to give a five-membered ring either in a sequential or a concerted manner (Scheme 2).

Table 2 Synthesis 2-Aryl-1-Arylmethyl-1*H*-benzimidazoles **3a–j** Using 10 mol% Oxalic Acid

Entry	Ar	Time (min)	Product	Yield (%)	Mp (°C)	
					Found	Lit.
1	Ph	35	**3a**	97	133–134	134[20]
2	4-Tol	35	**3b**	95	128–129	127–128[21]
3	4-$MeOC_6H_4$	35	**3c**	96	127–129	129–130[22]
4	2-$MeOC_6H_4$	30	**3d**	94	151–153	151[23]
5	4-ClC_6H_4	30	**3e**	98	137–138	136[22]
6	2-ClC_6H_4	25	**3f**	98	158–159	159[22]
7	2-$O_2NC_6H_4$	25	**3g**	99	120–121	120[22]
8	4-$O_2NC_6H_4$	20	**3h**	97	189–191	192[23]
9	4-$Me_2NC_6H_4$	35	**3i**	93	255–256	255[22]
10	2-furyl	40	**3j**	95	94–95	95–96[20]



Scheme 2 Proposed mechanism for the formation of disubstituted benzimidazoles

We also explored the synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6** using oxalic acid as a catalyst. These types of compounds are biologically important due to their inhibitory activities of P38MAP kinase, fungicides, herbicides, and plant growth regulators[15] and synthetically important due to the use of substituted imidazoles in ionic liquids,[16] which have given a new approach to 'green chemistry'.

Several synthetic methods are available for the preparation of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6** using benzil (**5**) or benzoin (**7**), ammonium acetate, aromatic aldehydes and various acid catalysts.[17] We have used oxalic acid as a catalyst for the synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6** from benzil (**5**), aromatic aldehydes, and ammonium acetate (Scheme 3). The reaction conditions were standardized for the preparation of 2,4,5-triphenyl-1*H*-imidazole (**6a**), which was isolated in 98% yield using 10 mol% oxalic acid with ethanol–water (1:1) as the solvent. The methodology was extended to a range of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6b–f** using various aromatic aldehydes (Table 3), which were isolated in moderate to excellent yields (86–98%).

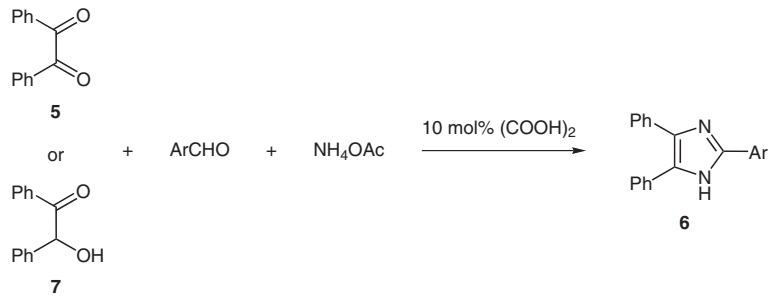
1,2-Diketones (like benzil) are usually prepared from α-hydroxy ketones (like benzoin) catalyzed by various oxidants. Some of these catalysts are toxic, costly, and require tedious experimental procedures.[18] To avoid the preparation of the 1,2-diketone, the synthesis of 2,4,5-triphenyl-1*H*-imidazole (**6a**) was studied using benzoin (**7**). Surprisingly, using similar reaction conditions, **6a** was isolated in 94% yield. Encouraged by this result, we extended the methodology by using benzoin (**7**) and various aromatic aldehydes to synthesis of various 2-aryl-4,5-diphenyl-1*H*-imidazoles **6b–f** which were obtained in 65–96% yield.

The proposed mechanism for the synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6** from benzil (**5**), aromatic aldehydes, and ammonium acetate by oxalic acid catalysis may be the same as that of acid-catalyzed synthesis (Scheme 4).[19a] Using benzoin (**7**), aromatic aldehydes substrates, and ammonium acetate with iodine as a catalyst,[19b] the proposed mechanism includes initial oxidation of benzoin to benzil in the presence of iodine followed by similar mechanism as that for benzil. But, in the present method, since oxalic acid is the most oxidized product, this possibility is discarded. On heating benzoin with 10 mol% oxalic acid in ethanol–water the formation of benzil was not observed, and it was also not formed by aerial oxidation. Herein, we propose a mechanism for oxalic acid catalyst, which involves the formation of a diamine intermediate **8** that condenses with benzil and undergoes intramolecular cyclization to give a dihydroimidazole intermediate **9**. The intermediate **9** then undergoes aerial oxidation to give the fully conjugated system **10**, which may be the driving force for this step. Subsequently, **10** rearranges via a [1,5]sigmatropic proton shift to afford the corresponding 2-aryl-4,5-diphenylimidazoles such as **6a** (Scheme 4).

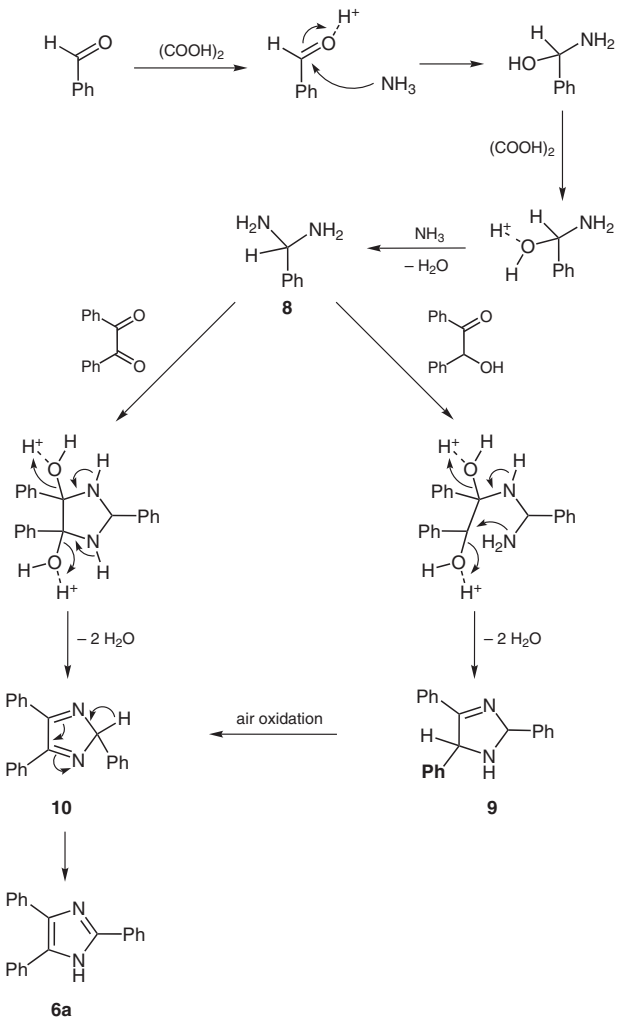
Using 10 mol% oxalic acid catalyst, 2-aryl-1-arylmethyl-1*H*-benzimidazoles **3** and 2-aryl-4,5-diphenyl-1*H*-imidazoles **6** were efficiently synthesized in moderate to excellent yields. The better selectivity was observed for synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles **3**.

Table 3 Synthesis 2-Aryl-4,5-diphenyl-1*H*-imidazoles **6** Using Benzil or Benzoin, Ammonium Acetate, Aromatic Aldehydes, and 10 mol% Oxalic Acid

Entry	Ar	Time (min)		Product	Yield (%)	
		Benzil	Benzoin		Benzil	Benzoin
1	Ph	30	65	**6a**	98	94
2	4-ClC_6H_4	30	70	**6b**	95	96
3	4-$MeOC_6H_4$	35	70	**6c**	96	93
4	4-$O_2NC_6H_4$	50	95	**6d**	86	65
5	4-HOC_6H_4	40	65	**6e**	93	92
6	4-$Me_2NC_6H_4$	35	70	**6f**	97	89



Scheme 3 Synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles **6**



Scheme 4 Probable mechanism for the formation of triarylimidazoles using benzil or benzoin, ammonium acetate, aromatic aldehydes, and oxalic acid catalyst

For all the presented reactions, ethanol–water solvent was used, which is relatively environmentally benign and supporting 'green chemistry'. The advantages of the reported method are the use of an inexpensive and readily available catalyst, easy workup, and improved yields.

^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer using TMS as internal standard. Mass spectra were taken with Micromass - QUATTRO-II of WATER mass spectrometer. HPLC was performed using Zorbax SB-C18 reverse phase column (0.46 × 25 cm) on Shimadzu instrument equipped with an automatic injector with UV-PDA detector. Detection was carried out at 254 nm. The mobile phase consists of 0.05% TFA–MeCN (1:1). The products were eluted at flow rate of 1 mL/min using isocratic method. Flash column chromatography was performed with 300–400 mesh silica gel and analytical TLC was performed on precoated silica gel plates (60F-254). Melting points were determined in capillary tubes and are uncorrected.

1-Aryl-2-arylmethyl-1*H*-benzimidazoles 3; General Procedure

A mixture of oxalic acid (10 mol%) and *o*-phenylenediamine (10 mmol) was dissolved in EtOH–H_2O (1:1, 20 mL) and aromatic aldehyde (20 mmol) was added and the mixture was stirred at 80 °C until completion (TLC). The mixture was cooled to r.t. and poured into ice-water (50 mL). A solid precipitated that was collected by filtration and washed with H_2O and then dried to give the corresponding 1,2-disubstituted benzimidazole.

1-Benzyl-2-phenyl-1*H*-benzimidazole (3a)

Off-white solid; mp 133–134 °C; HPLC purity: 98.1%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.3 (s, 2 H), 7.1 (d, *J* = 8.2, 2 Hz, 2 H), 7.1–7.25 (m, 6 H), 7.35–7.40 (m, 3 H), 7.6 (dd, *J* = 8.2, 2 Hz, 2 H), 7.8 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 284 $[M + H]^+$.

1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-benzimidazole (3b)

White solid; mp 128–129 °C; HPLC purity: 96.8%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.39 (s, 3 H), 5.39 (s, 2 H), 6.98 (d, *J* = 8 Hz, 2 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.19 (m, 2 H), 7.24 (d, *J* = 8 Hz, 2 H), 7.28 (m, 1 H), 7.58 (d, *J* = 8 Hz, 2 H), 7.85 (m, 1 H).

MS (EI, 70 eV): *m*/*z* = 312 $[M + H]^+$.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (3c)

White solid; mp 127–129 °C; HPLC purity: 98.2%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 3.83 (s, 3 H), 5.37 (s, 2 H), 6.84 (d, *J* = 8 Hz, 2 H), 6.94 (d, *J* = 9 Hz, 2 H), 7.02 (d, *J* = 9 Hz, 2 H), 7.20 (m, 2 H), 7.30–7.23 (m, 1 H), 7.62 (d, *J* = 9 Hz, 2 H), 7.83 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 344 $[M + H]^+$.

1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-benzimidazole (3d)

White solid; mp 151–153 °C; HPLC purity: 95.6%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H), 3.76 (s, 3 H), 5.23 (s, 2 H), 6.69 (dd, *J* = 7, 1 Hz, 1 H), 6.75 (t, *J* = 7 Hz, 1 H), 6.81 (d, *J* = 8 Hz, 1 H), 6.93 (d, *J* = 8 Hz, 1 H), 7.03 (t, *J* = 8 Hz, 1 H), 7.29–7.12 (m, 4 H), 7.43 (dd, *J* = 8, 2 Hz, 1 H), 7.53 (dd, *J* = 8, 2 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 344 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzimidazole (3e)

White solid; mp 137–138 °C; HPLC purity: 97.6%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (s, 2 H), 7.02 (d, *J* = 9 Hz, 2 H), 7.19 (d, *J* = 8 Hz, 1 H), 7.36–7.24 (m, 4 H), 7.43 (m, 2 H), 7.58 (m, 2 H), 7.86 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 353 $[M + H]^+$.

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-benzimidazole (3f)

White solid; mp 158–159 °C; HPLC purity: 94.8%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s, 2 H), 6.62 (dd, *J* = 8, 1 Hz, 1 H), 7.05 (td, *J* = 8, 1 Hz, 1 H), 7.36–7.12 (m, 6 H), 7.52–7.38 (m, 3 H), 7.89 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 353 $[M + H]^+$.

1-(2-Nitrobenzyl)-2-(2-nitrophenyl)-1*H*-benzimidazole (3g)

White solid; mp 120–121 °C; HPLC purity: 96.7%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (s, 2 H), 6.95 (dd, *J* = 7, 1 Hz, 1 H), 7.15 (dd, *J* = 8, 1 Hz, 1 H), 7.30 (td, *J* = 8, 1 Hz, 1 H), 7.37 (td, *J* = 8, 1 Hz, 1 H), 7.56–7.43 (m, 3 H), 7.73–7.65 (m, 2 H), 7.87 (dd, *J* = 8, 1 Hz, 1 H), 8.20–8.12 (m, 2 H).

MS (EI, 70 eV): *m*/*z* = 374 $[M + H]^+$.

1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzimidazole (3h)
White solid; mp 189–191 °C; HPLC purity: 98.3%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (s, 2 H), 7.19 (dd, *J* = 8, 1 Hz, 1 H), 7.28 (d, *J* = 9 Hz, 2 H), 7.35 (td, *J* = 9, 1 Hz, 1 H), 7.41 (td, *J* = 7, 1 Hz, 1 H), 7.84 (d, *J* = 9 Hz, 2 H), 7.93 (dd, *J* = 8, 1 Hz, 1 H), 8.24 (d, *J* = 8 Hz, 2 H), 8.33 (d, *J* = 9 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 374 $[M + H]^+$.

1-[4-(Dimethylamino)benzyl]-2-[4-(dimethylamino)phenyl]-1*H*-benzimidazole (3i)
White solid; mp 255–256 °C; HPLC purity: 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (s, 6 H), 2.93 (s, 6 H), 5.59 (s, 2 H), 6.70–6.55 (m, 4 H), 6.96 (d, *J* = 9 Hz, 2 H), 7.70–7.05 (m, 3 H), 7.55 (d, *J* = 9, 2 Hz, 2 H), 7.73 (d, *J* = 8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 370 $[M + H]^+$.

2-(2-Furyl)-1-(2-furylmethyl)-1*H*-benzimidazole (3j)
White solid; mp 94–95 °C; HPLC purity: 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (s, 2 H), 6.21 (dd, *J* = 3, 1 Hz, 1 H), 6.26 (dd, *J* = 3, 2 Hz, 1 H), 6.59 (dd, *J* = 4, 2 Hz, 1 H), 7.20 (dd, *J* = 3, 1 Hz, 1 H), 7.31–7.25 (m, 3 H), 7.51–7.44 (m, 1 H), 7.62 (dd, *J* = 2, 1 Hz, 1 H), 7.82–7.75 (m, 1 H).

MS (EI, 70 eV): *m*/*z* = 264 $[M + H]^+$.

2,4,5-Triaryl-1*H*-imidazoles 6; General Procedure
A mixture of oxalic acid (10 mol%), NH_4OAc (40 mmol), and benzil or benzoin (10 mmol) was dissolved in EtOH–H_2O (1:1, 20 mL) and aromatic aldehyde (12 mmol) was added. The mixture was heated at 80 °C until completion (TLC). The mixture was cooled to r.t., poured into ice-water (50 mL) and the solid that precipitated was collected by filtration, washed with H_2O, and dried to give the 2,4,5-triaryl-1*H*-imidazole.

2,4,5-Triphenyl-1*H*-imidazole (6a)
Off-white solid; mp 276–277 °C; HPLC purity: 98%.

^{1}H NMR (400 MHz, DMSO): δ = 7.55–7.68 (m, 6 H), 7.72–7.75 (m, 3 H), 7.9–7.95 (m, 6 H), 8.8 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 296 $[M + H]^+$.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (6b)
Off-white solid; mp 264–364 °C; HPLC purity: 95.5%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5–7.65 (m, 6 H), 7.68–7.72 (m, 2 H), 7.9–8.0 (m, 6 H), 8.7 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 330 $[M + H]^+$.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (6c)
Off-white solid; mp 241–243 °C; HPLC purity: 96.6%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.9 (s, 3 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.5–7.65 (m, 4 H), 7.75 (m, 2 H), 7.85–7.95 (m, 6 H), 8.7 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 326 $[M + H]^+$.

2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (6d)
Off-white solid; mp 131–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5–7.65 (m, 4 H), 7.68–7.72 (m, 4 H), 7.9–8.0 (m, 4 H), 8.25 (d, *J* = 8.1 Hz, 2 H), 8.9 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 341 $[M + H]^+$.

2-(4-Hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole (6e)
Off-white solid; mp 256–257 °C; HPLC purity: 97.1%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.3 (br s, 1 H), 7.55–7.60 (m, 6 H), 7.65–7.72 (m, 2 H), 7.9–8.0 (m, 6 H), 8.7 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 312 $[M + H]^+$.

2-[4-(Dimethylamino)phenyl]-4,5-diphenyl-1*H*-imidazole (6f)
Off-white solid; mp 259 –260 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.9 (s, 6 H), 7.1 (d, *J* = 8.2 Hz, 2 H), 7.4–7.55 (m, 4 H), 7.65–7.7 (m, 2 H), 7.8–7.95 (m, 6 H), 8.7 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* = 339 $[M + H]^+$.

Acknowledgement

The authors are thankful to the Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad - 431004 (MS), India for the providing laboratory facility.

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