Polysubstituted Imidazoles as LysoTracker Molecules: Their Synthesis via Iodine/H₂O and Cell-Imaging Studies

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ABSTRACT: An iodine-catalyzed, environmentally benign one-pot methodology has been developed for the synthesis of diverse substituted imidazoles. This transition-metal-free, aerobic, water-mediated cyclization reaction is operationally simple and works well with different amines or aldehydes by multiple C−N bond formations with satisfactory yield. The methodology is regioselective as well as scalable. These imidazole derivatives show excellent fluorescence properties both in the solid and solution phase, which is further extended to live-cell imaging. Due to the suitable fluorescence properties of these scaffolds, lysosome-directing groups are incorporated in two of these derivatized imidazoles to track intracellular lysosomes. Successfully, those molecules show bright blue fluorescence while detecting lysosomes in human or murine cells and can be considered to be rapid lysosome-staining probes.

INTRODUCTION

Imidazoles are the most important privileged nitrogen-containing heterocyclic scaffolds present in many natural products and pharmaceutical drugs (Figure 1).¹⁻⁵ They are known to exhibit a broad range of biological activities, such as anticancer, antimicrobial, antihypertensive, and protein kinase inhibitor properties.⁶⁻¹⁰ Apart from these activities, imidazole-containing molecules are also reported to exhibit fluorescence properties. These properties are further utilized in metal sensing, biological imaging applications, and organic light-emitting diodes (OLEDs).¹¹⁻¹⁵ A lysosome is an important organelle in eukaryotic cells that is involved in the degradation of foreign internalized particles. Lysosomes also play an active role in autophagy, cellular metabolism and recycling. Thus, it becomes an important candidate for immunological research, where the resolution of infection is often dependent on lysosome-mediated degradation of engulfed pathogens by phagocytic immune cells, such as macrophages and neutrophils. Lysosome-dependent processing of pathogens is also related to antigen display and antibody production.¹⁶ These organelles are involved in many cellular signaling functions, including intracellular transport, cell antigen processing, and the initiation of apoptosis.¹⁷,¹⁸ Lysosomes are acidic, membrane-bound organelles (pH ≤ 5) present in cells. Dysfunctions of lysosomes have been implicated in several diseases, such as tumour generation and neurodegenerative diseases.¹⁶ Selective probing of these organelles with small fluorescent molecules has been reported recently, and further, these probes are useful to reveal the underlying mechanism behind the cause of diseases.¹⁹

In the previous literature, these imidazole molecules were synthesized using transition-metal-catalyzed approaches, with transition metals such as copper, palladium, silver, etc., but these synthetic approaches practically have several drawbacks,
such as moisture and air sensitivity, requirement of careful handling, hazardous and harsh conditions, heavy metal poisoning, and scale-up difficulties. These synthetic limitations have alerted chemists to find new environment-friendly pathways to construct small organic molecules. In view of the above considerations, metal-free organic reactions have gained much importance and have undergone alterations in both industry and academia. Studies revealed that molecular iodine has the ability to functionalize C–H bonds to form new C–C and also C–heteroatom bonds. Iodine has also gained much attention in synthetic organic methodologies due to its low toxicity, metal-like characteristics, environmentally benign nature, and ease of handling in the laboratory, making it more suitable as a catalyst. Accordingly, iodine serves as an alternative catalyst instead of transition metals in many organic reactions. In recent times, several organic reactions have been effectively scrutinized in water medium to avoid organic solvents due to their toxic nature. As water is a non-flammable, non-hazardous, non-volatile, and nontoxic solvent, nature drives all reactions in aqueous medium. In the face of severe environmental pollution due to various toxins, the "green chemistry" methodology is now a very popular approach. For this reason, synthetically more straightforward and convergent reactions taking water as the green reaction medium is of key interest at present. Therefore, because of the worldwide demand for environmentally benign organic syntheses, and our continuing research interest in developing strategies for iodine-catalyzed small heterocycle synthesis, herein we developed aerobic iodine-catalyzed oxidative Csp3–H functionalization from readily available starting materials to synthesize highly substituted imidazoles in the aqueous medium.

### Table 1. Optimization of the Reaction Conditions

| entry | catalyst (mol %) | base (3 equiv) | solvent | temp (°C) | oxidant | yield (%) 3a |
|-------|-----------------|----------------|---------|-----------|---------|-------------|
| 1     | I2 (20)         | H2O            | rt      | air       |         | 32          |
| 2     | I2 (30)         | H2O            | rt      | air       |         | 38          |
| 3     | I2 (40)         | H2O            | rt      | air       |         | 39          |
| 4     | I2 (30)         | H2O            | 50      | air       |         | 62          |
| 5     | I2 (30)         | H2O            | 60      | air       |         | 65          |
| 6     | I2 (30)         | H2O            | 70      | air       |         | 71          |
| 7     | I2 (30)         | H2O            | 80      | air       |         | 71          |
| 8     | I2 (30)         | K2CO3          | H2O     | 70        | air     | 94          |
| 9     | I2 (30)         | NaHCO3         | H2O     | 70        | air     | 69          |
| 10    | I2 (30)         | Na2CO3         | H2O     | 70        | air     | 74          |
| 11    | I2 (30)         | Cs2CO3         | H2O     | 70        | air     | trace       |
| 12    | I2 (30)         | TEA            | H2O     | 70        | air     | trace       |
| 13    | I2 (30)         | DBU            | H2O     | 70        | air     | trace       |
| 14    | I2 (30)         | pyridine       | H2O     | 70        | air     | trace       |
| 15    | I2 (30)         | K2CO3          | H2O     | 70        | N2-atm  | 0           |
| 16    | I2 (30)         | K2CO3          | H2O     | 70        | air     | 0           |
| 17    | KI              | K2CO3          | H2O     | 70        | air     | trace       |
| 18    | KI              | K2CO3          | H2O     | 70        | air     | trace       |

**Reaction conditions:** 1a (0.5 mmol, 1 equiv), 2a (1.0 mmol, 2 equiv), catalyst (0.15 mmol, 0.3 equiv) in solvent (2.0 mL) for 6 h; H2O = water, rt = room temperature.
Interestingly, all of these molecules show good fluorescence properties. We further utilized these properties to visualize lysosomes in live cells. Considering the acidic nature of lysosomes, two molecules bearing a weak basic group were selected from the series and studied for selective lysosome tracking. Observations revealed that these molecules could permeate into cells and selectively go into the targeted lysosome, giving blue fluorescence. Thus, it can be an added value for organelle-targetable fluorescent probes (OTFPs).

**RESULTS AND DISCUSSION**

To identify the optimal reaction conditions, easily accessible benzil (1a) and benzylamine (2a) were selected as model substrates for the optimization of the reaction (Table 1). The initial screening reaction began with the treatment of 1a and 2a with 20 mol % iodine in water at room temperature (rt) under open-air conditions for 6 h, affording the desired product 1-benzyl-2,4,5-triphenyl-1H-imidazole (3a) in 32% yield. Increasing the amount of iodine to 30 mol % provided the desired product 3a in 38% yield. The yield did not change remarkably with a further increase in the amount of iodine to 40 mol % (entries 1−3). Temperature screening revealed that 70 °C was optimal for the desired transformation (entries 4−6) and further increasing the temperature resulted in no improvement of the yield (entry 7). Different bases were then scrutinized to improve the yield, and K2CO3 was found to be the best one with maximum yield of up to 94% (entries 8−14).

There was no product formation observed in the presence of N2 atmosphere (entry 15) and without the catalyst (entry 16), respectively. Other iodine catalysts, such as tetrabutylammonium iodide (TBAI) and KI, were not efficient in this protocol (entries 17 and 18). From the studies, the reaction of 1a (1 equiv) with 2a (2 equiv) with 30 mol % iodine in water (2 mL) under open-air conditions at 70 °C for 6 h (entry 8) was established as the optimal reaction conditions. A previous literature study revealed that an α-hydroxy ketone (benzoin)
could be oxidized to a diketone (benzil) in the presence of an oxidant, and hence, benzoin was also used in this methodology.38

With the best reaction conditions in hand, the scope of this methodology was studied thoroughly with a diverse range of amines bearing electron-releasing and electron-deficient groups. As shown in Scheme 2, the reactions were very clean and the desired imidazoles were observed in satisfactory yield. Substitution of amine on the phenyl ring containing an electron-neutral (4-H), electron-donating (4-Me, 4-t-Bu), and electron-withdrawing (4-CF3) group successfully took place under the above reaction conditions, producing the desired product in good yield (Scheme 2, entries 3a/3a−/3c/3cb and 3g/3g). Under the optimal reaction conditions, different
diketone was introduced in the reaction to test the feasibility of alkyl diketones with satisfactory yield (product in the case of unsymmetrical diketones, including aryl compound and S61, Supporting Information (SI)). Further con copy and mass spectrometry. The exact structure of synthesized imidazoles were characterized by NMR spectros with good responses (Scheme 2, entries 3hb and entries 3h)

This methodology produced exclusively one regioisomer  of the unsymmetrical imidazole was further structure of the unsymmetrical imidazole was further

Table 2. Gram-Scale Synthesis

| diketone | α-hydroxy ketone | amines/ aldehyde | product from diketone | yield from diketone (%) | product from α-hydroxy ketone | yield from α-hydroxy ketone (%) |
|---------|-----------------|-----------------|----------------------|-------------------------|-----------------------------|---------------------------------|
| 1a      | 2a              | 3a              | 88                   |                         | 3i   | 73                             |
| 1b’     | 2i              |                  |                      |                         | 3p   | 78                             |
| 1b’     | 2i              |                  |                      |                         |                  |                                 |
| 4a      | 2a              | 5a              | 76                   |                         | 3l   |                                 |
| 1a      | 7e              | 8e              | 66                   |                         |                  |                                 |

Scheme 7. Reaction in the Presence of Radical Capture Reagents

halogen-substituted amines underwent a smooth conversion affording the corresponding imidazoles in moderate yields, which gave chances for further functionalization (Scheme 2, entries 3d/3dβ−3f/3fβ). The scope of this methodology was again estimated using amines that contain trifluoromethoxy (−OCF3), naphthyl, and heterocyclic moieties (Scheme 2, entries 3h/3hβ, 3l/3lβ, and 3i/3iβ−3k/3kβ). The trifluoromethoxy amine offered the desired imidazoles 3h (78% yield) and 3kβ (71% yield), and naphthyl amine provided 3l (77% yield) and 3lβ (75% yield), respectively. Heterocyclic amines, including pyridyl, and other amines successfully underwent a smooth conversion, furnishing the corresponding imidazoles 3i/3iβ−3k/3kβ in good to moderate yields (Scheme 2). The versatility of the methodology was checked with the α-hydroxy ketone, 2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone (1b’). The optimized reaction conditions facilitated smooth conversion with different amines, including heterocyclic amines with good responses (Scheme 2, entries 3o and 3p). All of the synthesized imidazoles were characterized by NMR spectroscopy and mass spectrometry. The exact structure of 3l was further confirmed by X-ray single-crystal analysis (see p S60 and S61, Supporting Information (SI)).

This methodology produced exclusively one regioisomer product in the case of unsymmetrical diketones, including aryl alkyl diketones with satisfactory yield (5a−d, Scheme 3). The structure of the unsymmetrical imidazole was further confirmed by a single-crystal X-ray diffraction study of compound 5a (see p S63 and S64, SI). Next, an aliphatic diketone was introduced in the reaction to test the feasibility of the protocol, but unfortunately, the reaction did not proceed (Scheme 4).

Encouraged by these results, we turned our attention to three-component reactions to extend the scope and practicability of the methodology. While surveying the previous literature, many reports were found based on three-component reactions for triaryl-substituted imidazole synthesis. In this work, the three-component reaction was examined using diketone/α-hydroxy ketone (1a/b), aromatic aldehydes (7a−g), and ammonium acetate. Here, aromatic aldehydes and ammonium acetate were used instead of benzylamine. Several aldehydes containing electron-donating and electron-withdrawing groups provided the desired triaryl-substituted imidazoles in moderate to good yield (8a−g, Scheme 5). Moreover, the reaction of 2-hydroxy-1,2-bis(4-methoxyphenyl)ethan-1-one (anisoin) (1b’) was examined by reacting with pyridine-2-carbaldehyde (7e) and ammonium acetate producing the desired 8h in 78% yield (Scheme 5).

After successful achievement of the synthesis of triaryl-substituted imidazoles, the versatility of this one-pot reaction protocol was further tested for the synthesis of tetraaryl-substituted imidazoles. Thus, the diketone/α-hydroxy ketone (1a/1b), aromatic aldehyde (7b), aromatic amine (9a), and ammonium acetate successfully reacted with each other to furnish the corresponding product satisfactorily (Scheme 6, entry 10a).

After examining the reaction scope, the span of the flexibility of this protocol was successfully extended to the gram-scale level for benzil (1a), benzoin (1b), anisoin (1b’), and aryl alkyl
ketone (4a) with different amines, including heterocyclic ones. In each case, satisfactory results were observed (Table 2).

After a successful evaluation of the reaction scope, the mechanistic aspect of the methodology was next investigated. To establish the mechanism, some experiments were performed. Initially, benzil (1a) and benzylamine (2a) reacted with each other under the optimized reaction conditions in the presence of radical capture reagents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT), which proceeded smoothly to form the product 3a in 93 and 92% yield, respectively, indicating the reaction may not proceed through a radical mechanism pathway (Scheme 7). Thereafter, some control experiments were performed (Scheme 8). α-Hydroxy ketone (1b′) was oxidized to the diketone product (1c) in the presence of iodine (Scheme 8i). The diketone product 1c then reacted with amine (2a) to give the addition product A (isolated and characterized), followed by cyclization to give the final product (3o) (Scheme 8).

Based on the above control experiments and with supporting references, a plausible mechanism is proposed for the formation of both tri- and tetrasubstituted imidazoles in Scheme 9. For tetrasubstituted imidazole formation, initially, the α-hydroxyl ketone (A) is oxidized to a diketone (B) in the presence of iodine.42 Next, the diketone (B) is converted to the addition product (C) via simple addition with amine (2 equiv) (2). Two equivalents of aryl/heteroaryl amine form the Schiff base on both carbonyls in dicarbonyl compounds (Scheme 9B), making the addition product (Scheme 9C), whereas 1 equiv of aryl/heteroaryl amine forms the Schiff base only at the selected carbonyl centre in dicarbonyl compounds that form the desired product, oxazole derivatives.37 This addition product forms two possible anionic intermediates (D and G) in the presence of base (K₂CO₃). Here, we expect that the formation of two regioisomers is possible, but only one regioisomer is formed in the reaction medium. It is suspected that the anionic stability of these intermediates limits the reaction to the formation of only one regioisomer in the case of the unsymmetrical diketone. The stable anionic intermediate (D) further undergoes iodine-catalyzed oxidative cyclization to yield the desired product.

For tri/tetraaryl-substituted imidazole formation, initially, the α-hydroxyl ketone (1b) is oxidized to a diketone (1a). Then, in situ generated ammonia from ammonium acetate43 will react via two pathways, i.e., path C and path D, to give the desired triaryl- and tetraaryl-substituted imidazoles, respectively. In path C, ammonia reacts with the aldehyde to form a diamine intermediate (H). This diamine intermediate (H) is added to 1a to give an imino intermediate (I),44 which upon proton transfer gives the triaryl-substituted imidazoles (9). In path D, the aldehyde, aromatic amine, and ammonia form intermediate J. Finally, this intermediate J reacts with 1a to form tetraaryl-substituted imidazoles (12).

Next, the photophysical properties of tri- and tetrasubstituted imidazole derivatives were explored. Substituted imidazole derivatives showed good fluorescence responses in the blue range when irradiated at 365 nm. Fluorescence of some selected imidazole derivatives was recorded in dimethyl sulfoxide (DMSO) (Figure 2) and is reported in this paper. It was observed that the imidazole derivatives containing electron-donating groups (i.e., OH, NMe₂) as well as highly conjugated groups (i.e., naphthyl) exhibited increased fluorescence responses (Figure 2: 3l, 8c, and 8f). Among them, 3l, 8c, and 8f showed the best fluorescence responses. Solid-state fluorescence of selected compounds was captured by irradiating at 365 nm.
The bright blue fluorescence of these polysubstituted imidazoles encouraged us to explore their application as biological intracellular probes. Accordingly, some derivatives were preinstalled with lysosome-directing groups into the parent compound as a lysosome-detecting probe. We explored the possible applications of the fluorescence properties of two

Scheme 9. Plausible Mechanism

Plausible mechanisms:
A: Formation of tetrasubstituted imidazoles

B: Formation of tetra/triaryl substituted imidazoles

Figure 2. (A) Fluorescence spectra of some selected imidazole derivatives (500 nM) in DMSO (λex = 290–330 nm). (B) Fluorescence of 10 μM DMSO solution of selected compounds captured by irradiating at 365 nm. (C) Solid-state fluorescence of selected compounds captured by irradiating at 365 nm.
selected molecules for imaging lysosomes in a representative human cervical cancer cell line (HeLa) and a murine macrophage cell line (J774A.1). Two compounds, $8e$ and $8f$, having strong fluorescence properties in the UV ($4',6$-diamidino-2-phenylindole (DAPI)) channel were preinstalled with lysosome-directing groups.

Both HeLa and J774A.1 cells were mixed separately with these compounds along with a commercially available lysosome-specific stain, the LysoTracker Red DND-99 dye (100 nmol), and incubated for 30 min at 37 °C. Stained HeLa cells were subsequently fixed with paraformaldehyde, while murine macrophages (J774A.1) were observed without any fixation. In both cell lines, the compounds were found to be membrane-permeant and localized within the cytoplasm (Figure 3). Although the compounds fluoresced in the DAPI channel, signals from the blue channel were converted to a green color to easily observe their localization inside cells.

Intracellular localization of our synthesized molecules and the LysoTracker Red DND-99 dye was compared in both cell lines. Confocal microscopy revealed that both compounds $8e$ and $8f$ were localized in the same compartment as LysoTracker Red (Figure 3) with high Pearson’s correlation coefficient values (greater than 0.5). Also, the macrophage cell morphology was not affected due to incubation with a higher concentration of compounds. These compounds were used to successfully observe lysosomes in living as well as fixed cells, and cellular distributions of the dyes were also not affected by paraformaldehyde-based fixation.

**CONCLUSIONS**

In summary, we have successfully developed a transition-metal-free, environmentally benign method for the synthesis of both tetra- and trisubstituted imidazoles from readily available starting materials via an iodine-catalyzed areal oxidative one-pot reaction in water for the first time. This method with no toxic byproducts has advantages such as peroxide- and organic-solvent-free reactions. The mild procedure is cost-effective, atom-economic, and scalable. Thus, it is more practically applicable. In addition, this synthetic methodology was successfully employed at the gram-scale level. Some of these imidazole derivatives also showed excellent fluorescence responses. Two such synthesized molecules $8e$ and $8f$ were modified with lysosome-directing groups and were found to be successfully colocalized with LysoTracker Red in cell-imaging studies having very high Pearson coefficient values, and hence, these two molecules are new additions to organelle-targetable fluorescent probes. Therefore, we believe that the current methodology produces some very useful polysubstituted imidazole derivatives by an environmentally benign method.

**EXPERIMENTAL SECTION**

**General Information.** All of the necessary chemicals and organic solvents that were utilized for the methodology were acquired from Sigma-Aldrich, Thermo Fischer Scientific, and TCI chemicals. These were used without additional purification unless otherwise noted. The melting point of the final imidazole derivatives was determined using a one side open capillary tube. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F$_{254}$ aluminum TLC sheets. The developed chromatogram was visualized by
UV absorbance. For purification of the crude imidazole mixture, silica gel (100–200 and 230–400 mesh) was utilized for column chromatographic separations. The structure of the tetra- and trisubstituted imidazoles was confirmed using $^1$H NMR, $^{13}$C NMR, electron ionization (EI)-mass, and electrospray ionization (ESI)-mass spectrometry studies. NMR spectra of the imidazole derivatives were recorded on a Bruker 600 MHz spectrometer and a JEOL RESONANCE 400 MHz spectrometer. Deuterated NMR solvents, CDCl$_3$ and DMSO-$d_6$, were utilized for recording NMR spectra and tetramethylsilane (TMS) was used as the internal standard.

Chemical shifts ($\delta$) are given in parts per million (ppm) relative to TMS ($\delta = 0.00$). The coupling constants ($J$) of the NMR spectra are expressed in hertz (Hz). All copies of $^1$H and $^{13}$C NMR spectra are attached in the Supporting Information. High-resolution mass spectrometry (HRMS) $(m/z)$ and ESI mass data analysis were performed using EI techniques (JEOL-JMS 700 spectrometer) and an LCQ-ORBITRAP-XL instrument, respectively. For solving the crystal structure of the selected imidazole derivatives (3l and 5a), a Bruker Kappa Apex II X-ray crystallography instrument was used. Singlet (s), doublet (d), double doublet (dd), triplet (t), and multiplet (m) were used for describing $^1$H NMR multiplicity patterns.

**Spectroscopic Measurements.** Spectroscopic grade DMSO solvent was used for preparing the solutions of imidazole derivatives. A Shimadzu UV-1800 spectrophotometer was used for recording the UV–vis absorption spectra of the selected imidazole derivatives. A Hitachi F-7000 fluorescence spectrophotometer was used for recording the fluorescence spectra of the mentioned imidazole derivatives. High-quality quartz cuvettes were utilized while recording the fluorescence spectra at room temperature.

**Synthetic Procedures.**

**General Experimental Procedure for the Preparation of 1,2,4,5-Tetrasubstituted Imidazoles (3a–p, 5a–d).** 1,2,4,5-Tetrasubstituted imidazoles were prepared by a one-pot reaction using a mixture of benzil (1a)/benzoin (1b) (0.50 mmol, 1 equiv) and the corresponding amine (2a–n) (1 mmol, 2 equiv) in water (2 mL) medium. The reaction was carried out by taking iodine (0.15 mmol, 0.3 equiv, 380.8 mg) as a catalyst in open air at 70 °C for 6 h. The complete conversion of the reactants into desired products was checked by TLC, and the reaction mixture was allowed to cool to room temperature. Then, a solid appeared, which was treated with 10% aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$) solution to remove the excess iodine from the reaction mixture. The aqueous phase was then extracted with ethyl acetate (EtOAc). Anhydrous Na$_2$SO$_4$ was used to dry the combined organic layers and filtered, followed by concentration using a rotary evaporator under a low pressure. Column chromatography (silica gel, 100–200 mesh) was used to purify the crude mixture eluting with EtOAc and petroleum ether to afford the desired triaryl-substituted imidazoles (8a–h).

**General Experimental Procedure for the Preparation of Triaryl-Substituted Imidazoles (8a–h).** Triaryl-substituted imidazoles were prepared using a one-pot reaction methodology taking a mixture of readily available starting materials, benzil (1a)/benzoin (1b) (0.50 mmol, 1 equiv), different substituted aromatic aldehydes (7a–h) (0.5 mmol, 1 equiv), and ammonium acetate (1 mmol, 2 equiv, 154.17 mg) in water (2 mL) medium. Molecular iodine (0.15 mmol, 0.3 equiv, 38.08 mg) was utilized as a catalyst here under open-air conditions at 70 °C for 6 h. The complete conversion of the reactants was checked by TLC. The reaction mixture was then allowed to cool to room temperature. Subsequently, a solid appeared, which was treated with 10% aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$) solution to remove the excess iodine from the reaction mixture. The aqueous phase was then extracted with ethyl acetate (EtOAc). Anhydrous Na$_2$SO$_4$ was used to dry the combined organic layers and filtered, followed by concentration using a rotary evaporator under a low pressure. Column chromatography (silica gel, 100–200 and 230–400 mesh) was used to purify the crude mixture eluting with EtOAc and petroleum ether to afford the desired triaryl-substituted imidazoles (8a–h).

**General Experimental Procedure for the Preparation of the Tetraaryl-Substituted Imidazole (10a).** The tetraaryl-substituted imidazole was prepared using a one-pot reaction methodology taking a mixture of readily available starting materials, benzil (1a)/benzoin (1b) (0.50 mmol, 1 equiv), aromatic aldehyde (7b) (0.5 mmol, 1 equiv), aromatic amine (9a) (0.5 mmol, 1 equiv), and ammonium acetate (1 mmol, 2 equiv, 154.17 mg) in water (2 mL) medium. In particular, molecular iodine (0.15 mmol, 0.3 equiv, 38.08 mg) was used as a catalyst in open air at 70 °C for 6 h. The complete conversion of the reactants was checked by TLC. The reaction mixture was then allowed to cool to room temperature. Subsequently, a solid appeared, which was treated with 10% aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$) solution to remove the excess iodine from the reaction mixture. Ethyl acetate (EtOAc) was used to extract the aqueous phase and anhydrous Na$_2$SO$_4$ was used to dry the combined organic phases. The combined organic phase was then filtered, followed by concentration using a rotary evaporator under a very low pressure. Column chromatography (silica gel, 100–200 mesh) was used to purify the crude mixture eluting with ethyl acetate (EtOAc) and petroleum ether to afford the desired tetraaryl-substituted imidazole product (10a).

**General Experimental Procedure for Scaling Up to the Gram Level for Tetrasubstituted Imidazoles (3a, 3i, 3p, and 5a).** The gram-scale level reactions were carried out by taking a mixture of diketone (1a/4a)/$\alpha/\beta$-hydroxy ketone (1b/b’) (5 mmol, 1 equiv) and the amine (2a and 2i) (10 mmol, 2 equiv) in H$_2$O (20 mL) in open air at 70 °C for 6 h. Molecular iodine (1.5 mmol, 0.3 equiv, 380.8 mg) was used as a catalyst for this transformation. The complete consumption of the reactants was checked by TLC. After that the reaction mixture was allowed to cool to room temperature. Subsequently, a solid appeared. The solid was further treated with 10% aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$) to remove extra iodine from the reaction mixture. The aqueous phase was then extracted with ethyl acetate (EtOAc) and the combined organic phase was then dried with anhydrous Na$_2$SO$_4$. The dried organic phase was then filtered and concentrated using a rotary evaporator under a low pressure. The crude mixture was then purified by column chromatography (silica gel, 100–200 and 230–400 mesh) with EtOAc and petroleum ether to get the desired triaryl-substituted imidazole products 3a, 3i, 3p, and 5a.

**General Experimental Procedure for Scaling Up to the Gram Level for the Triaryl-Substituted Imidazole (8e).** The triaryl-substituted imidazole was prepared by taking a mixture of benzil (1a) (5.0 mmol, 1 equiv), the aromatic aldehyde (7e) (5.0 mmol, 1 equiv), and ammonium acetate (1 mmol, 2 equiv, 154.17 mg) in H$_2$O (20 mL) in open air and heating the reaction mixture at 70 °C for 6 h. Molecular iodine (1.5 mmol, 0.3 equiv, 380.8 mg) was used as a catalyst. The end point of the reaction was determined by checking TLC.
appeared after allowing the reaction mixture to cool to room temperature. Then, 10% aqueous sodium thiosulfate (Na2S2O3) solution was used to wash the reaction mixture to remove the excess iodine. EtOAc was used to extract the aqueous phase. Then, the combined organic phase was dried with anhydrous Na2SO4. The dried organic part was filtered with a rotary evaporator under reduced pressure. Subsequently, column chromatography (silica gel, 100−200 mesh) was used to purify the crude mixture utilizing EtOAc and petroleum ether as the eluent to afford the desired product (8e).

**Cell Lines and Cell Culture.** A human cervical cancer cell line (HeLa) was acquired from the National Centre for Cell Science, Pune, India, and was used in the study. Cells were cultivated in Iscove’s modified Dulbecco’s medium (IMDM), supplemented with 10% fetal calf serum and 1% antibiotic, antimycotic solution and maintained at 37 °C under 5% CO2 and 95% air.

**Microscopy.** HeLa cells (5000) were seeded on sterilized grease-free coverslips and incubated overnight at 37 °C. The synthesized molecules (8e and 8f) were added to the culture medium at the following concentrations. After 10 min, a 1:1 EtOAc/petroleum ether (60−80 °C) was used to wash the reaction mixture and concentrated using a rotary evaporator under reduced pressure. Then, 10% aqueous sodium thiosulfate (Na2S2O3) solution was used to wash the reaction mixture and concentrated using a rotary evaporator under reduced pressure. Subsequently, column chromatography (silica gel, 100−200 mesh) was used to purify the crude mixture utilizing EtOAc and petroleum ether as the eluent to afford the desired product (8e).

**1-(4-Fluoro-benzyl)-2-(4-fluoro-phenyl)-4,5-diphenyl-1H-imidazole (3d).** White solid; yield (3d) 80% and (3d) 76%; Rf = 0.49 [15% EtOAc/petroleum ether (60−80 °C)]; m.p. 144−146 °C; 1H NMR (CDCl3 600 MHz): δ 7.68 (s, 2H), 7.45−7.41 (m, 5H), 7.30 (s, 4H), 7.19 (s, 2H), 7.12 (s, 1H), 6.99 (t, J = 8.4 Hz, 2H), 6.75 (s, 2H), 5.11 (s, 2H). 13C{1H} NMR (CDMSO-d6, 150 MHz): δ 163.6, 162.4, 162.0, 160.8, 146.6, 137.3, 134.8, 133.8, 133.7, 131.3, 131.3, 130.9, 130.6, 129.5, 129.4, 128.6, 128.3, 128.2, 127.7, 126.8, 126.5, 116.2, 116.1, 115.9, 115.8, 47.5; HRMS (EI+) m/z: calcd: C22H16F2N2 (M + H+): 342.1673, found: 342.1676.

**1-(4-Bromo-benzyl)-2-(4-bromo-phenyl)-4,5-diphenyl-1H-imidazole (3e).** Off-white solid; yield (3e) 82% and (3e) 78%; Rf = 0.37 [10% EtOAc/petroleum ether (60−80 °C)]; m.p. 128−130 °C; 1H NMR (CDCl3 600 MHz): δ 7.57−7.54 (m, 4H), 7.39−7.36 (m, 2H), 7.36−7.34 (m, 2H), 7.23−7.21 (m, 2H), 7.17−7.15 (m, 1H), 6.67 (d, J = 8.4 Hz, 2H), 5.03 (s, 2H). 13C{1H} NMR (CDCl3 150 MHz): δ 146.8, 138.5, 138.3, 134.0, 132.8, 132.0, 131.9, 130.7, 130.6, 130.5, 130.3, 129.6, 129.1, 129.0, 128.2, 127.6, 126.8, 126.7, 126.3, 123.5, 121.5, 47.8; HRMS (EI+) m/z: calcd: C22H16Br2N2 (M + H+): 543.0071, found: 543.0075.

**1-(4-Chloro-benzyl)-2-(4-chloro-phenyl)-4,5-diphenyl-1H-imidazole (3f).** White solid; yield (3f) 86% and (3f) 81%; Rf = 0.46 [15% EtOAc/petroleum ether (60−80 °C)]; m.p. 160−162 °C; 1H NMR (CDCl3 600 MHz): δ 7.58−7.55 (m, 4H), 7.39−7.38 (m, 3H), 7.36−7.34 (m, 2H), 7.23−7.19 (m, 6H), 7.17−7.15 (m, 1H), 6.73 (d, J = 8.4 Hz, 2H), 5.06 (s, 2H). 13C{1H} NMR (CDCl3 150 MHz): δ 146.8, 138.4, 135.7, 135.2, 134.0, 133.4, 131.0, 130.6, 130.2, 129.2, 129.0, 129.0, 128.9, 128.2, 127.3, 126.8, 126.7, 47.7; HRMS (EI+) m/z: calcd: C22H16Cl2N2 (M + H+): 454.1004, found: 454.1015.
119.5, 47.8; HRMS (EI) m/z: calcd: C_{26}H_{20}N_{4}O (M+) 388.1688, found: 388.1669.

2-Benzyl[1,3]dioxol-5-yl-1-benzo[1,3]dioxol-5-ylmethyl-4,5-diphenyl-1H-imidazole (3j). White solid; yield (3j 81% and 3k 76%); Rf = 0.52 [20% EtOAc/petroleum ether (60–80 °C)]; m.p. 144–146 °C; H NMR (CDCl₃, 600 MHz): δ 7.80–7.83 (m, 2H), 7.60–7.62 (m, 2H), 7.49–7.51 (m, 2H), 7.41–7.43 (m, 2H), 7.29–7.31 (m, 2H), 7.18–7.20 (m, 2H), 5.36 (s, 2H), 3.72 (s, 3H), 3.51 (s, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 153.6, 150.7, 144.5, 138.4, 134.8, 134.3, 132.5, 131.2, 131.0, 130.5, 129.0, 128.9, 128.0, 127.6, 127.2, 126.9, 126.6, 126.5, 125.4, 125.1, 44.0; HRMS (ESI+) m/z: calcd: C_{26}H_{28}N_{2}O_{4} (M+H) 439.1858, found: 439.1852.

5c [20% EtOAc/petroleum ether (60–80 °C)]; m.p. 144–146 °C; H NMR (CDCl₃, 600 MHz): δ 7.75–7.77 (m, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.38–7.36 (m, 3H), 7.33–7.38 (m, 2H), 7.20 (t, J = 7.8 Hz, 2H), 5.24 (s, 2H), 2.32 (s, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 147.6, 137.9, 131.7, 135.3, 130.9, 129.1, 128.9, 128.8, 128.4, 127.6, 127.4, 126.4, 125.7, 124.9, 101.6; HRMS (ESI+) m/z: calcd: C_{26}H_{28}N_{2}O_{4} (M+H) 439.1852, found: 439.1856.

2-[(4-Methoxy-phenyl)-2-[(4-methoxy-phenyl)-5-methyl-4-phenyl-1H-imidazole (5a). White solid; yield (5a 90%); Rf = 0.51 [15% EtOAc/petroleum ether (60–80 °C)]; m.p. 112–114 °C; δ 7.77 (d, J = 7.2 Hz, 2H), 7.59–7.57 (m, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.38–7.36 (m, 3H), 7.20 (t, J = 7.8 Hz, 2H), 5.24 (s, 2H), 2.32 (s, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 147.6, 137.9, 131.7, 135.3, 130.9, 129.1, 128.9, 128.8, 128.4, 127.6, 127.4, 126.4, 125.7, 124.9, 101.6; HRMS (ESI+) m/z: calcd: C_{26}H_{28}N_{2}O_{4} (M+H) 439.1856, found: 439.1857.

2-(4-Methoxy-phenyl) -3-(4,3-dimethoxy-phenyl) -2-phenyl-1H-imidazole (5c). White solid; yield (5c 86%); Rf = 0.43 [20% EtOAc/petroleum ether (60–80 °C)]; m.p. 144–146 °C; H NMR (CDCl₃, 600 MHz): δ 7.64–7.63 (m, 2H), 7.46–7.39 (m, 5H), 7.31–7.27 (m, 4H), 7.20 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 7.8 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.67 (m, 1H), 6.63 (dd, dd, J = 8.4 Hz, 1H, 1H), 5.21 (s, 2H), 3.66 (s, 3H), 3.37 (s, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 149.0, 148.6, 147.3, 139.6, 138.5, 134.8, 133.7, 133.1, 132.5, 131.2, 129.8, 129.6, 129.4, 129.1, 128.9, 128.0, 127.6, 127.0, 126.5, 125.4, 125.1, 44.0; HRMS (ESI+) m/z: calcd: C_{26}H_{28}N_{2}O_{4}Cl (M+H) 481.1683, found: 481.1685.

2-(4-Chloro-phenyl) -3-(4,3-dimethoxy-phenyl) -1-(pyridin-2-ylmethyl)-1H-azido-2-ylpyridine (5d). Light yellow solid; yield (5d 81%); Rf = 0.48 [40% EtOAc/petroleum ether (60–80 °C)]; m.p. 178–180 °C; H NMR (CDCl₃, 600 MHz): δ 8.43–8.41 (m, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.84 (td, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.64 (td, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.43–7.42 (m, 2H), 7.32–7.26 (m, 4H), 7.19–7.17 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.72–6.71 (m, 1H), 6.65 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H), 5.95 (s, 2H), 3.67 (s, 3H), 3.37 (s, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 158.2, 150.5, 149.4, 149.2, 148.7, 148.6, 138.4, 137.5, 137.2, 136.8, 134.5, 134.3, 133.7, 133.1, 129.8, 129.7, 127.2, 123.3, 123.0, 122.5, 121.7, 120.8;
113.8, 111.9, 55.7, 55.4, 51.1; HRMS (ESI+) m/z: calcd: C_{21}H_{15}N_3O_Cl(M + H^+): 348.1588, found: 348.1591.

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (8a). White solid; yield (8a 73% and 8b 70%); R_f = 0.48 [30% EtOAc/petroleum ether (60–80 °C)]; m.p. 272–274 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 12.77 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.55–7.53 (m, 5H), 7.50–7.48 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H). ^13C{1H} NMR (DMSO-d_6, 150 MHz): δ 144.8, 137.7, 135.4, 132.3, 131.2, 129.6, 129.1, 129.0, 128.9, 128.6, 128.3, 127.5, 127.3, 127.0; HRMS (ESI+) m/z: calcd: C_{21}H_{15}N_3O_Cl (M + H^+): 348.1592, found: 348.1592.

4-(5-Diphenyl-1H-imidazol-2-yl)-benzaldehyde (8g). White solid; (8g 77% and 8h 70%); R_f = 0.44 [40% EtOAc/petroleum ether (60–80 °C)]; m.p. 188–190 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 13.00 (s, 1H), 10.02 (s, 1H), 8.29 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.31 (m, 2H), 7.24 (m, 4H). ^13C{1H} NMR (DMSO-d_6, 150 MHz): δ 129.2, 144.6, 138.5, 135.9, 135.8, 135.2, 131.1, 130.5, 130.0, 129.7, 129.0, 128.7, 128.5, 127.5, 127.2, 125.8; HRMS (ESI+) m/z: calcd: C_{21}H_{16}O (M + H^+): 325.1341, found: 325.1341.

1-(4-Amino-3-biphenylamino)-1-(4,5-diphenyl-1H-imidazol-2-yl)-pyridine (8h). Light yellow solid; yield (8h 78%); R_f = 0.50 [40% EtOAc/petroleum ether (60–80 °C)]; m.p. 246–248 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 12.93 (s, 1H), 8.57 (d, J = 4.4 Hz, 1H), 8.08 (d, J = 4.4 Hz 1H), 7.84 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 4H), 7.33–7.30 (m, 1H), 6.67 (s, 4H), 3.72 (s, 4H). ^13C{1H} NMR (DMSO-d_6, 150 MHz): δ 141.5, 137.6, 130.3, 129.0, 128.3, 128.2, 127.5, 126.9, 125.6; HRMS (ESI+) m/z: calcd: C_{21}H_{15}N_2O (M + H^+): 313.1002, found: 313.1004.

1-(4-Bromo-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (10a). White solid; yield (10a 86% and 10a 82%); R_f = 0.58 [15% EtOAc/petroleum ether (60–80 °C)]; m.p. 244–246 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 7.53 (d, J = 8.4 Hz, 2H), 7.48–7.46 (m, 2H), 7.41–7.37 (m, 4H), 7.33–7.32 (m, 3H), 7.25–7.22 (m, 6H), 7.18 (t, J = 7.2 Hz, 1H). ^13C{1H} NMR (DMSO-d_6, 150 MHz): δ 145.4, 137.5, 136.2, 143.5, 143.7, 137.2, 131.8, 131.6, 131.2, 130.5, 129.4, 129.1, 128.9, 128.6, 128.1, 127.6, 127.2, 126.1, 114.3, 113.9, 55.6; HRMS (ESI+) m/z: calcd: C_{21}H_{18}BrClN_2 (M + Na^+): 485.0420, found: 485.0415.

1,2-Bis-(4-methoxyphenyl)ethane-1,2-dione (1c). Yellow solid; yield (1c 92%); R_f = 0.52 [10% EtOAc/petroleum ether (60–80 °C)]; m.p. 140–142 °C; ^1H NMR (CDCl_3, 600 MHz): δ 7.93 (d, J = 9.0 Hz, 4H), 6.95 (d, J = 9.0 Hz, 4H), 3.86 (s, 6H). ^13C{1H} NMR (CDCl_3, 150 MHz): δ 193.5, 164.8, 132.3, 126.2, 114.3, 55.6; HRMS (ESI+) m/z: calcd: C_{21}H_{18}O_3 (M + Na^+): 293.0790, found: 293.0801.

Benzyl-[2-benzylamino]-1,2-bis-(4-methoxy-phenyl)-ethylidene-amine (A). Yellow solid; yield (A 86%); R_f = 0.56 [15% EtOAc/petroleum ether (60–80 °C)]; m.p. 246–248 °C; ^1H NMR (CDCl_3, 600 MHz): δ 7.77 (d, J = 9.0 Hz, 4H), 7.35 (d, J = 4.2 Hz, 8H), 7.30–7.26 (m, 2H), 6.91 (d, J = 9.0 Hz, 4H), 4.63 (d, J = 5.4 Hz, 4H), 3.84 (s, 6H). ^13C{1H} NMR (CDCl_3, 150 MHz): δ 167.0, 162.2, 138.4, 128.8, 128.8, 127.9, 127.6, 126.6, 113.8, 55.4, 44.1; HRMS (ESI+) m/z: calcd: C_{20}H_{18}N_2O_2(M + H^+): 449.2229, found: 449.2241.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00934.

Copies of ^1H NMR and ^13C NMR spectra for all imidazole derivatives; X-ray crystal data of compounds 3l and 5a (PDF)

X-ray crystallographic data file of benzylamine (CIF)
X-ray crystallographic data file of naphthyl amine (CIF)
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